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AUGUST 31, 1982

INDUSTRIAL HYGIENE REPORT

TITLE

Industrial Hygiene and Toxicological
Review of the Screwworm Adult Suppression
System (SWASS)
Mission, Texas

FILE NUMBER

TR 82-7

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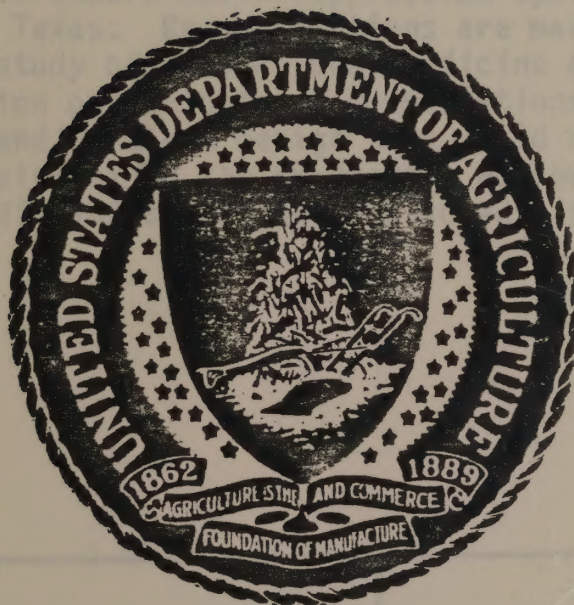
August 31, 1982

INDUSTRIAL HYGIENIST(S)

INDUSTRIAL HYGIENE AND TOXICOLOGICAL
REVIEW OF THE SCREWORM ADULT SUPPRESSION
SYSTEM (SWASS)
MISSION, TEXAS

ABSTRACT

A summary is presented of industrial hygiene survey findings and toxicity of the chemicals used in the Screwworm Adult Suppression System (SWASS) production operations in Mission, Texas. Recommendations are made to obtain peer review and/or further study. Areas of the production process are also made to seek production techniques and to reduce the need for personal protective equipment and to reduce the risk of pest stress. Further study should be continued.



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UNITED STATES DEPARTMENT OF AGRICULTURE
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SAFETY AND HEALTH MANAGEMENT DIVISION

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Industrial Hygiene and Toxicological
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INDUSTRIAL HYGIENIST(S)

John Teske

TYPE REPORT

Survey and Literature Review

ABSTRACT

A summary is presented of industrial hygiene survey findings and toxicity of the chemicals used in the Screwworm Adult Suppression System (SWASS) production operations in Mission, Texas. Recommendations are made to obtain peer review and/or further study of occupational medicine and toxicological aspects of the production operations. Recommendations are also made to seek production techniques and/or plant design that would reduce the need for personal protective equipment of the production worker and to reduce the risk of heat stress. Periodic industrial hygiene surveys should be continued.

DISTRIBUTION

APHIS

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**The Industrial Hygiene and Toxicological Review of
The Screwworm Adult Suppression System
Production Facilities, Mission, Texas**

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SUMMARY

The industrial hygiene and toxicological review of the Screwworm Adult Suppression System (SWASS) production and dispersion facilities has been an on-going process starting in July 1979, when the production facilities at Mission, Texas were first surveyed. At that time, the manufacturing of SWASS was evolving from a pilot plant to a production operation. During February 1980, initial industrial hygiene monitoring was conducted to characterize the nature of employee exposures to the SWASS ingredients. This consisted of monitoring the ambient work environment and the plant effluent. The results of the preliminary monitoring were forwarded for review in May 1980 to the APHIS National Veterinary Services Laboratory. The results of this review were received in August 1980 from the laboratory. During June 1980, monitoring was conducted on the SWASS dispersing aircraft to determine the pilot and disperser exposures selected SWASS ingredients. A summary report of all these activities was submitted to APHIS in May 1981. In July 1981, a meeting was held at APHIS to review that report. During October 1981, additional industrial hygiene monitoring was conducted at the SWASS plant to obtain more specific information on personal breathing zone exposures of the more volatile SWASS ingredients. The rationale for this approach to monitoring is that if the more volatile air contaminants are controlled, then all worker exposures will be maintained at a healthful level. The interim results of that survey were submitted to APHIS in January 1982. Since the January 1982 report, an intensive review of the literature was conducted and summarized regarding the toxicological aspects of each of the SWASS chemical ingredients. These summaries are contained later on in this report, and copies of most of the relevant literature are contained in the appendices. In addition, a study was conducted during June 1982 to assess the effectiveness of the respirators being used during SWASS production. The results of that study are contained in a separate report (TR 82-8). Heat stress measurement indicate a continuing need for periodic rest periods and the air conditioned rest facility.

The present plant should be considered an intermediate step to a plant where SWASS can be produced without the extensive reliance on personal protective equipment including respirators. The current reliance on respirators to protect worker health is contrary to current industry practices and not in compliance with OSHA regulations. The OSHA regulations require that when ever current technology permits, the protection of worker health should be provided through engineering controls, such as equipment enclosures and positive local exhaust ventilation. It is believed that technology exists to provide the enclosures and ventilation to protect worker health and it should be utilized in SWASS production.

Some concerns that have evolved from the industrial hygiene and toxicological review of the SWASS program include uncertainty regarding the potential health effects from chronic exposure of production workers to the SWASS chemicals in addition to their chronic toxicity. There also remains a question regarding the synergistic effect of the multiple chemical exposures. Previous reports have included recommendations to minimize employee exposure through the extensive use of personal protective equipment and medical monitoring. Currently this is being done. A suggested re-design of the production facilities with positive ventilation has been made that should substantially reduce potential exposure to the SWASS ingredients during manufacturing and hopefully eliminate or reduce the need for personal protective equipment. The re-design was also suggested to bring the plant into compliance with OSHA regulations. Other recommendations include the utilization of an industrial toxicologist and occupational physician to review the work done to date, and that periodic industrial hygiene surveys be conducted to monitor the SWASS program.

Recommendations

1. This report should be submitted for peer review by an occupational physician and an industrial toxicologist to:
 - a. Review this report to substantiate the conclusions regarding toxicity of the SWASS ingredients and to review the medical monitoring program.
 - b. Suggest or provide other information not contained in this report that could enhance the knowledge of the toxicological properties of the SWASS ingredients, or improve the medical monitoring program.
 - c. Suggest or recommend additional measures that can be implemented to protect the health of employees who are producing SWASS.
2. The efforts should be continued to streamline and enclose the production facilities and to provide positive local exhaust ventilation to minimize employee exposure to the SWASS ingredients, taking into consideration the suggestions and recommendations evolving from item number one above, as well as information contained in this report. This is essential to bring the plant into compliance with the OSHA regulations.
3. The present program of medical monitoring, personal protective equipment and work practices should be continued until such time that the outside review discussed in item one above or the plant re-design discussed in item two above indicates a need for changes.

4. The present work/rest cycle of approximately 50 percent work and 50 percent rest should be continued during the hot summer months. The air conditioned rest facility should also be continued. Also, during the hot summer months, work activities should be performed in shady areas and workers should be allowed to rest if the heat stress becomes excessive.
5. Industrial hygiene surveys should be continued on a semi-annual basis.

SWASS Production

SWASS is a bait-toxicant-attractant system for adult screwworms which is used in conjunction with the sterile screwworm fly releases to control the screwworm fly population. The SWASS system is composed of two parts. One part is the attractant or wormlure and the other part is the toxicant. Wormlure consists of chemical ingredients shown in Table 1.

Composition of Wormlure and the percentage of each of the 11 compounds in the mixture

TABLE 1

Chemical compound	Percentage
acetic acid (glacial)	14.0
benzoic acid	2.7
butyric acid	12.8
valeric acid	12.6
indole	2.6
iso-butanol	10.6
sec-butanol	10.8
Phenol	11.6
p-cresol	11.0
dimethyl disulfide	11.5

The wormlure is combined with the balance of the SWASS ingredients including the toxicant to form the completed system. The composition of the completed system is shown in Table 2 below.

The percentage of each ingredient used in the Screwworm Adult Suppression System (SWASS)

TABLE 2

Ingredient	Percentage
Dried whole blood	30.5
Sucrose	30.5
Swormlure ¹	23.6
Corn cob grits	7.5
KSL wax ²	5.9
Vapona (DDVP, Dichlorvos)	2.0

1 Swormlure and KSL are mixed together.

2 KSL wax is made by American Hoechst Inc.

A copy of the finished product label is show in Figure 1. The use of SWASS is tightly controlled by USDA.

SWASS production operations are located in a one story open air building at the USDA facility near Mission, Texas. Production equipment consists of mixers, pelitezer, conveyors, scales, bagging and sealing equipment. The final product is a pellet one inch long and one-half inch in diameter. Dispersion of the pellet is usually by aircraft. Cold storage for the bagged finished pellets is adjacent to the production facility to minimize volatilization and loss of effectiveness. Figure 2 is a sketch of the current SWASS manufacturing facility.

A two shift operation is currently employed for the manufacture of SWASS. The first shift of six employees mixes by hand the swormlure chemicals and wax which is then stored. The second shift of six employees adds the insecticide and the dry ingredients to the swormlure which after blending is pelletized, bagged and stored in refrigerated trailers. The basic steps in the manufacturing process are:

First Shift

1. Mix swormlure chemicals by hand.
2. Check quality with laboratory analysis.
3. Add heated wax in buckets.
4. Store buckets for next shift.

Second Shift

1. Add DDVP to corn cob grits.
2. Blend all ingredients in Hobert mixer.

Figure 1

FOR DISTRIBUTION AND USE ONLY WITHIN TEXAS

SWASS Pellets**SCREWWORM ADULT SUPPRESSION SYSTEM**

ACTIVE INGREDIENTS	BY WEIGHT
2.2 dichlorovinyl dimethyl phosphate	2.00%
SWORMLURE - 2 (Attractant)	22.20%
BAIT and INERT	75.80%
TOTAL	100.00%

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

KEEP OUT OF REACH OF CHILDREN**DANGER**

Dichlorvos insecticide is poisonous if swallowed, inhaled, or absorbed through skin or eyes. Do not get in eyes, on skin or on clothing. Do not breathe fumes. Wear clean rubber gloves, and face shield or goggles when handling the technical product. Keep all unprotected persons out of operational area. During commercial or prolonged exposure to technical dichlorvos, wear a mask or respirator of a type approved by EPA for dichlorvos protection. In case of contact, wash immediately with soap and water. Wash hands before eating or smoking. Wash all contaminated clothing with soap and hot water before reuse.

DISPOSAL

Pesticide that cannot be used should be disposed of in landfill approved for pesticides or buried in a safe place away from water supplies. Dispose container in an incinerator or landfill approved for pesticide containers or bury in a safe place.

FIRST AID TREATMENT AND ANTIDOTE STATEMENT

Atropine is the emergency antidote for DDVP poisoning. Call a physician immediately in all cases of suspected poison. If the material has been swallowed, induce vomiting immediately. If warning symptoms appear keep patient prone and quiet. Start artificial respiration immediately if patient is not breathing. Transport the patient immediately to the nearest hospital.

NOTE TO PHYSICIAN

WARNING SYMPTOMS: Symptoms include weakness, headache, tightness in chest, blurred vision, non-reactive pinpoint pupils, salivation, sweating, nausea, vomiting, diarrhea, and abdominal cramps. **TREATMENT:** Atropine is the specific therapeutic antagonist of choice against parasympathetic nervous stimulation. If there are signs of parasympathetic stimulation, atropine sulfate should be injected at 10 minute intervals, in doses of 1 to 2 milligrams, until complete atropinization has occurred. Morphine is contraindicated. Clear chest by postural drainage. Oxygen administration may be necessary. Observe patient continuously for 48 hours. Repeated exposure to cholinesterase inhibitors may, without warning, cause prolonged susceptibility to very small doses of cholinesterase inhibitor. Allow no further exposure until cholinesterase regeneration has been attained as determined by blood test. 2-PAM is also antidotal and may be administered conjunction with atropine.

DIRECTIONS FOR USE

SWASS is a bait-toxicant-attractant system for adult screwworms, *Cochliomyia hominivorax*. It is a complimentary screwworm suppression system which will be used in conjunction with sterile insect releases. In the event of major screwworm outbreaks in Texas aerial (rural areas) and ground (urban areas) releases of SWASS pellets will be used to reduce the screwworm population to the level that releases of sterile insects will effectively remove the remaining fertile flies. Also, SWASS is mainly effective against female screwworm flies, therefore application of SWASS pellets and release of sterile insects may be used simultaneously at times since the two suppression systems are compatible.

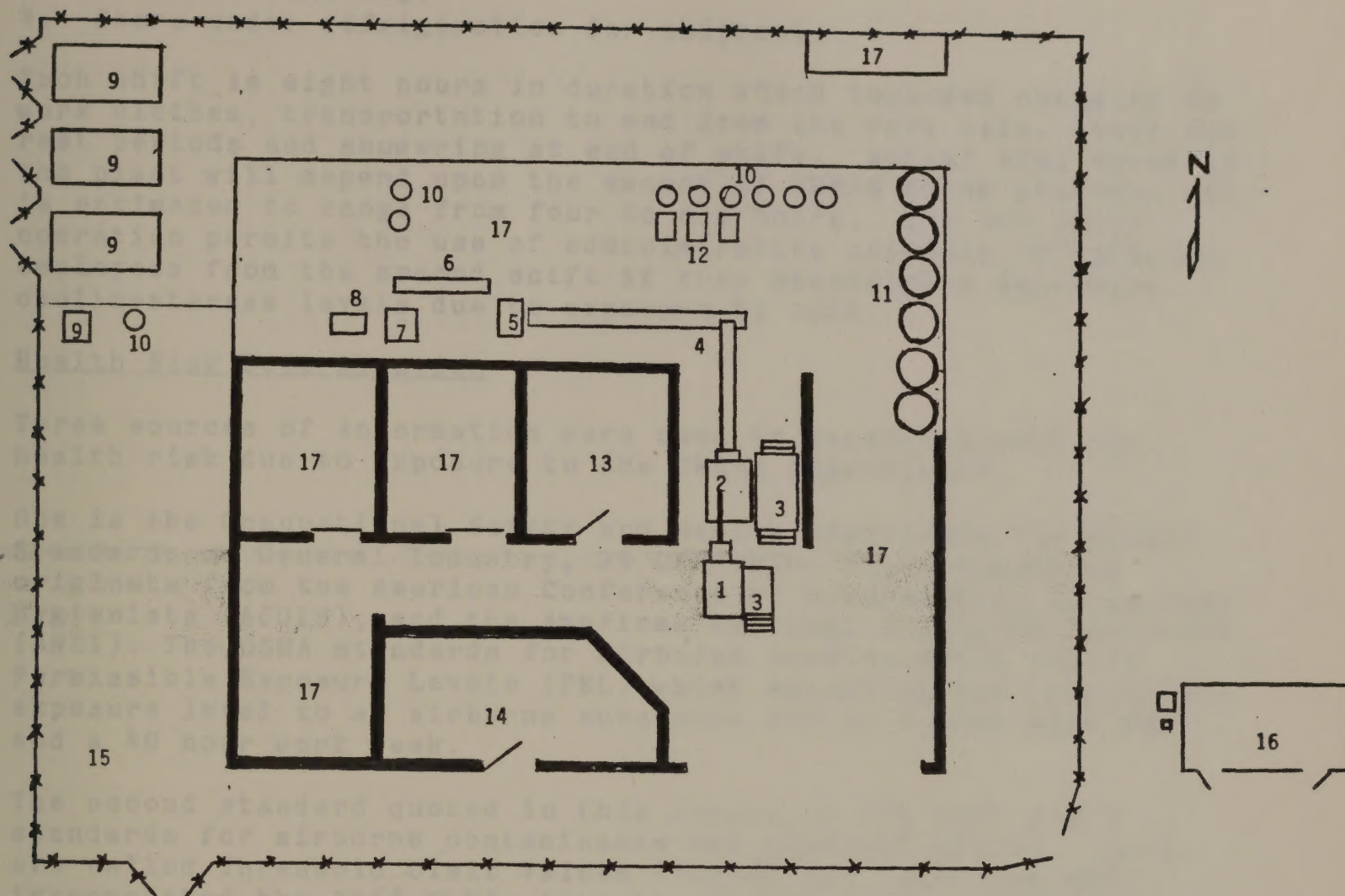
SWASS pellets should be used in Texas at the rate of 1 pound of pellets (150 pellets) per square mile. In most cases 2 applications of SWASS pellets per week for 2 weeks will be adequate to reduce screwworm populations to the desired level; however, during severe outbreaks additional applications may be required.

NOTE: This labeling must be in the possessions of the user at the time of pesticide application.

NOTE: This formulation is to be prepared, applied and monitored by approved federal employees only.

24(c) Registrant United States Department of Agriculture
AR SEA Screwworm Res Lab
P.O. Box 986
Mission, Texas 78572

EPA SLN NO. TX-780056



KEY

1. Blender
2. Pelletizer
3. Work Platform
4. Conveyors
5. Scale
6. Bag Sealer
7. Pallet
8. Forklift Truck
9. Refrigerated Storage
10. Liquid Chemical Drums
11. Wormlure Mixing Tanks
12. Wax Heaters
13. Restroom
14. Tool/Compressor Room
15. Used Drum Storage
16. Worker Rest Building
17. Dry Storage

Present SWASS Manufacturing Facility
Figure 2

3. Pelletize and bag.
4. Store under refrigeration for shipment.

Each shift is eight hours in duration which includes changing to work clothes, transportation to and from the work site, lunch and rest periods and showering at end of shift. Actual time spent in the plant will depend upon the amount of SWASS being produced and is estimated to range from four to six hours. The two shift operation permits the use of administrative controls of rotating employees from the second shift if they demonstrate depressed cholinesterase levels due to exposure to DDVP.

Health Risk Determination

Three sources of information were used to determine employee health risk due to exposure to the SWASS ingredients.

One is the Occupational Safety and Health Administration (OSHA) Standards of General Industry, 29 CFR 1910. These standards originate from the American Conference of Governmental Industrial Hygienists (ACGIH), and the American National Standards Institute (ANSI). The OSHA standards for airborne chemicals are called Permissible Exposure Levels (PEL) which establish the permissible exposure level to an airborne substance for an 8 hour work day and a 40 hour work week.

The second standard quoted in this report is the 1981 ACGIH standards for airborne contaminants and physical agents. These are called Threshold Limit Values (TLV's) and, although OSHA incorporated the 1968 TLV's into the 29 CFR 1910 mentioned above, subsequent TLV's do not carry the force of law. They do, however, represent the most current thinking in health hazards and are recognized as the preferred standard by USDA and other occupational health groups whenever they afford greater protection than the OSHA PEL. Most of the ACGIH information contained in the appendix of this report is taken from the "Documentation of the Threshold Limit Values" published by the ACGIH. Exposure values are expressed in terms of an 8 hour time weighed average (TWA) threshold limit values (TLV) which establishes an exposure limit for an 8 hour work shift and a 40 hour work week. Other aspects at a TLV include a 15 minute Short Term Exposure Limit (STEL) and a "Skin" notation for those substances readily absorbed through the skin. Ceiling values are sometimes established as TLV's for substances that have severe acute toxic effects.

The third source of information used in this report to determine employee health risk is the available literature used to prepare the toxicological review of the SWASS ingredients and to modify existing exposure levels or to propose new exposure levels where none existed. Copies of most of the literature referenced in this report can be found in the appendix. Where reports are too bulky to be included in the appendix, only a reference sheet is provided.

Industrial Hygiene Monitoring Protocols and Results

Workplace area and personal monitoring was conducted at various times to characterize the nature of exposures to the SWASS chemicals. For the purpose of efficiency and economy, monitoring focused on the most volatile or toxic chemicals to determine the magnitude of worker exposures and the effectiveness of controls. The rationale being that if these chemical exposures were controlled then all SWASS chemical exposures would be controlled. Table 3 contains a summary of monitoring protocols that were identified and, when applicable, used to determine chemical exposures. Table 4 contains a summary of all measurements obtained and other factors regarding the SWASS chemicals. In some instances the results shown in Table 4 are no longer applicable due to changes made in the production processes that have affected worker exposures. Therefore, as the SWASS production techniques are altered, industrial hygiene monitoring should be conducted to determine the impact on worker exposures. Monitoring should also be conducted semi-annually due to the potential adverse effect on the workers health due to exposure to the chemicals.

Medical Monitoring

The employees have pre-employment examinations as well as annual check ups at a local clinic. They also undergo cholinesterase testing on a bimonthly basis. If needed be, more frequent examinations and cholinesterase tests are conducted to identify potential health problems. The nature or frequency of medical monitoring has not been examined in great detail at the time that industrial hygiene surveys were conducted. It is therefore recommended that an occupational physician review existing medical protocols for adequacy in protecting the workers health, taking into consideration the chemical exposures, respiratory requirements and potential heat stress conditions.

SUMMARY OF EMPLOYEE MONITORING TECHNIQUES
FOR SWASS COMPONENTS

TABLE 3

Ingredient	TLV (2)	STEL (2)	PEL (3)	Collection/Analysis	Flow Rate	Sample Size	Reference
Acetic Acid	10 ppm 25 mg/M ³	15 ppm 37 mg/M ³	10 ppm 25 mg/M ³	Charcoal Tube/G.C.	0.2 to 1.0 $\frac{\text{liter}}{\text{min}}$	170 liters	NIOSH S169
Benzoic Acid	N/A	N/A	N/A	Glass Filter/G.C.	1.0 to 2.0 $\frac{\text{liter}}{\text{min}}$	204 to 480 liters	
Butyric Acid	N/A	N/A	N/A	Charcoal Tube/G.C.	0.2 to 1.0 $\frac{\text{liter}}{\text{min}}$	170 liters	Suggest NIOSH S169
P-Cresol	5 ppm 22 mg/M ³	N/A	5 ppm 22 mg/M ³	Silica Gel Tube/G.C.	50 to 200 $\frac{\text{ml}}{\text{min}}$	20 liters	NIOSH S167
DDVP	0.5 mg/M ³ (1) 0.1 ppm 1.0 mg/M ³	0.3 ppm 3.0 mg/M ³	1.0 mg/M ³	XAD-2 Tube/G.C.	1.0 $\frac{\text{liter}}{\text{min}}$	120 liters	NIOSH P&CAM 295
Dimethyl Disulfide	1.0 ppm ⁽¹⁾ 4.0 mg/M ³	1.5 ppm ⁽¹⁾ 6.0 mg/M ³	N/A	Chromosorb 104/G.C. two Tubes	10 to 25 $\frac{\text{ml}}{\text{min}}$	3 liters	NIOSH S350
Indole	0.07 ppm 0.3 mg/M ³ (1)	0.2 ppm ⁽¹⁾ 1.0 mg/M ³	N/A	Glass Filter/G.C.	1.0 to 2.0 $\frac{\text{liter}}{\text{min}}$	240 to 480 liters	Clayton
Iso-Butyl Alcohol	50 ppm 150 mg/M ³	75 ppm 225 mg/M ³	100 ppm 300 mg/M ³	Charcoal Tube/G.C.	50 to 200 $\frac{\text{ml}}{\text{min}}$	10 liters	NIOSH S64
Phenol	5 ppm 19 mg/M ³	10 ppm 38 mg/M ³	5 ppm 19 mg/M ³	0.1N NaOH Bubbler/G.C.	1.0 $\frac{\text{liter}}{\text{min}}$	100 liters	NIOSH S330
Sec-Butyl Alcohol	100 ppm 305 mg/M ³	150 ppm 955 mg/M ³	150 ppm 450 mg/M ³	Charcoal Tube/G.C.	50 to 200 $\frac{\text{ml}}{\text{min}}$	10 liters	NIOSH S53
Valeric Acid	5 ppm ⁽¹⁾ 20 mg/M ³	N/A	N/A	Charcoal Tube/G.C.	0.2 to 1.0 $\frac{\text{liter}}{\text{min}}$	170 liters	Suggest NIOSH S169
Nuisance Dust	10 mg/M ³	N/A	15 mg/M ³	PVC 5 um Filter/ Gravimetric	1.0 to 2.0 $\frac{\text{liter}}{\text{min}}$	240 to 480 liters	

(1) Proposed by USDA

(2) ACGIH

(3) OSHA

SUMMARY OF AIR SAMPLING RESULTS
SWASS PRODUCTION AND DISBURSING

TABLE 4

Chemical	Location/Individual	Type	Concentration	TLV/PEL ⁽²⁾⁽³⁾	Sample Date
Acetic Acid	Batch Mixing Area	Area	2.4 mg/M ³	25 mg/M ³	2/80
P-Cresol	Batch Mixing Area	Area	N.D. ⁽⁴⁾	22 mg/M ³	2/80
DDVP	Bagger	Personal	N.D.	0.5 mg/M ³ ⁽¹⁾	2/80
	Between Hobart & Portable Mixers	Area	N.D.	0.5 mg/M ³	2/80
	Behind Pellet Mill Operator	Area	N.D.	0.5 mg/M ³	2/80
	Between Hobart & Portable Mixers	Area	1.06 mg/M ³	0.5 mg/M ³	2/80
	Behind Pellet Mill Operator	Area	N.D.	0.5 mg/M ³	2/80
	Top of Hobart Mixer	Area	2.44 mg/M ³	0.5 mg/M ³	2/80
	Behind Pellet Mill Operator	Area	N.D.	0.5 mg/M ³	2/80
	Mixer	Personal	N.D.	0.5 mg/M ³	2/80
	Top of Bagging Machine Hopper	Area	1.28 mg/M ³	0.5 mg/M ³	2/80
	Between Portable & Hobart Mixers	Area	0.98 mg/M ³	0.5 mg/M ³	2/80
	John Teske	Personal	N.D.	0.5 mg/M ³	2/80
	C-45 Disbursing Station	Area	N.D.	0.5 mg/M ³	6/80
	C-45 Pilots Left Shoulder	Area	N.D.	0.5 mg/M ³	6/80
	C-45 SWASS Bag Storage	Area	0.043 mg/M ³	0.5 mg/M ³	6/80
	C-45 Copilot Seat/Cabin Door	Area	N.D.	0.5 mg/M ³	6/80
	Mixing/Pedro Cantu	Personal	2.49 mg/M ³	0.5 mg/M ³	10/81
	Mixing/Juan Luna	Personal	0.48 mg/M ³	0.5 mg/M ³	10/81
	Mixing/J. Renteria	Personal	0.939 mg/M ³	0.5 mg/M ³	10/81
	Pelletizing/A. Prado	Personal	0.148 mg/M ³	0.5 mg/M ³	10/81
	Bagging/A. Marez	Personal	0.234 mg/M ³	0.5 mg/M ³	10/81
	Bagging/V. Lopez	Personal	0.166 mg/M ³	0.5 mg/M ³	10/81

(2) TLV = ACGIH Threshold Limit Value
(3) PEL = OSHA Permissible Exposure Limit
(4) ND = Not Detected

Chemical	Location/Individual	Type	Concentration	TLV/PEL (2)(3)	Sample Date
Dimethyl Disulfide	Batch Mixing	Area	72.8 mg/M ³	4.0 mg/M ³ (1)	2/80
	C-45 Pilots Left Shoulder	Area	0.1 mg/M ³	4.0 mg/M ³ (1)	6/80
	C-45 Bag Storage	Area	0.006 mg/M ³	4.0 mg/M ³ (1)	6/80
	C-45 Disbursing Station	Area	0.022 mg/M ³	4.0 mg/M ³ (1)	6/80
	Mixing/J. Renteria	Personal	43.5 mg/M ³	4.0 mg/M ³ (1)	10/81
	Pelletizing/A. Prado	Personal	107 mg/M ³	4.0 mg/M ³ (1)	10/81
	Bagging/V. Lopez	Personal	66.2 mg/M ³	4.0 mg/M ³ (1)	10/81
	Bagging/F. Rodriquez	Personal	51.6 mg/M ³	4.0 mg/M ³ (1)	10/81
Indole	Behind Pellet Mill Operator	Area	N.D.	0.3 mg/M ³ (1)	2/80
	Down wind of mixer	Area	N.D.	0.3 mg/M ³	6/82
	Down wind of pelletizer	Area	N.D.	0.3 mg/M ³	6/82
Sec-Butanol	Batch Mixing	Area	15 mg/M ³	305/450 mg/M ³	2/80
	C-45 Pilots Left Shoulder	Area	N.D.	305/450 mg/M ³	6/80
	C-45 Disbursing Station	Area	N.D.	305/450 mg/M ³	6/80
	Mixing/Pedro Cantu	Personal	68.0 mg/M ³	305/450 mg/M ³	10/81
	Mixing/Juan Luna	Personal	24.3 mg/M ³	305/450 mg/M ³	10/81
	Mixing/J. Renteria	Personal	67.0 mg/M ³	305/450 mg/M ³	10/81
	Pelletizing/A. Prado	Personal	34.6 mg/M ³	305/450 mg/M ³	10/81
	Bagging/A. Marez	Personal	27.8 mg/M ³	305/450 mg/M ³	10/81
Iso Butanol	Batch Mixing	Area	36 mg/M ³	150/300 mg/M ³	2/80
	C-45 Pilots Left Shoulder	Area	N.D.	150/300 mg/M ³	6/80
	C-45 Disbursing Station	Areas	N.D.	150/300 mg/M ³	6/80
	Mixing/Pedro Cantu	Personal	154.8 mg/M ³	150/300 mg/M ³	10/81
	Mixing/Juan Luna	Personal	57.3 mg/M ³	150/300 mg/M ³	10/81
	Mixing/J. Renteria	Personal	163.7 mg/M ³	150/300 mg/M ³	10/81
	Pelletizing/A. Prado	Personal	80.2 mg/M ³	150/300 mg/M ³	10/81
	Bagging/A. Marez	Personal	55.6 mg/M ³	150/300 mg/M ³	10/81
Phenol	Batch Mixing	Area	N.D.	19.0 mg/M ³	2/80
	Batch Mixing	Area	N.D.	19.0 mg/M ³	2/80

- (1) Proposed by USDA
(2) TLV = ACGIH Threshold Limit Value
(3) PEL = OSHA Permissible Exposure Limit
(4) ND = Not Detected

Work Practices and Administrative Controls

Several work practices and administrative controls are used to limit worker exposure to the SWASS chemicals. One practice is to permit the workers to leave the area when they are not actually needed to produce SWASS. An air-conditioned rest shelter has been located adjacent to the production facility for this purpose. A second practice is the provision of showers that are used at lunch breaks and at the end of the shift. The showers are away from the production facility, as is the lunch area. No food consumption is permitted at the production facility. Hand washing facilities and a drinking fountain are also provided at the rest shelter. A third practice is the two shift schedule for SWASS production where worker exposure to DDVP is limited to the second shift. Then if employees demonstrate cholinesterase depression they can be assigned to the non-exposure first shift. Also, worker morale appears to be good and they are encouraged to suggest improvements in the plant operations.

Engineering Controls

The only one type of engineering control is being utilized to reduce worker exposure to the SWASS ingredients is the partial enclosure of the production operations with covers on the mixer and a screw conveyor to transport the SWASS to the pelletizer. An enclosed hopper is located at the foot of the screw conveyor. The hopper on the pelletizer and the conveyor to the bagging operation is open to the atmosphere. Natural ventilation is used to remove the various chemical vapors and dust. To the extent possible, the walls of the production building have been removed to facilitate the natural ventilation. The prevailing wind is such that dilution ventilation is, in most cases, provided from one direction parallel to the layout of the production equipment. The wind velocity depends upon weather conditions. Most recent measurements indicate velocities ranging from 400 fpm to an excess of 800 fpm (the limit of the velometer). Eventually, positive cross draft ventilation should be provided as shown in the sketch in Figure 3 since the existing natural ventilation is undependable and does not totally remove air contaminants from the workers breathing zone. With the proper plant lay out and ventilation, it should be possible to produce SWASS with the minimum of personnel protective equipment.

Personal Protective Equipment

Protective equipment for SWASS workers consists of both clothing and respirators. Clothing consists of high-top work boots, cotton coveralls, rubber gloves, and goggles. Several of the workers use shower caps to keep fugitive dusts from their hair. The cotton coveralls are laundered daily and a clean pair provided. Respirators used are American Optical with half face piece and dual R58 cartridges. Fresh cartridges are provided at the beginning of the work shift and after the lunch break. The personal protective clothing appears to be adequate to protect against skin contact with the chemicals. The adequacy of the respirators however, is in question due to the large number of chemicals the cartridges are required to remove from the atmosphere as well as an apparent drop in cholinesterase levels of some employees. A separate respirator real time quantitative fit test study is underway to determine the effectiveness of the respiratory protection. The results of that study will be reported separately and will dictate the future requirements for respiratory protection.

Exposure and Hazardous Substances

1910.1003 Air contaminants. "(a) To achieve compliance with paragraph (a) through (d) of this section (dealing with air contaminants) administrative or engineering controls must first be determined and implemented whenever feasible. When such controls are not feasible to achieve full compliance, protective equipment or any other protective measures shall be used to keep the exposure of employees to air contaminants within the limits prescribed in this section. Any electrical and/or mechanical measures used for this purpose must be approved for each particular use by a competent industrial hygienist or other technically qualified person. Whenever respirators are used, their use shall comply with 1910.134." (b) To achieve compliance with paragraph (e) through (g) of this section (dealing with air contaminants) administrative or engineering controls must first be determined and implemented whenever feasible. When such controls are not feasible to achieve full compliance, protective equipment or any other protective measures shall be used to keep the exposure of employees to air contaminants within the limits prescribed in this section. Any electrical and/or mechanical measures used for this purpose must be approved for each particular use by a competent industrial hygienist or other technically qualified person. Whenever respirators are used, their use shall comply with 1910.134."

Interpretation

The two preceding regulations simply state that if there are air contaminants in the workplace in excess of the permissible exposure limits the contamination must be reduced or eliminated at its source if at all possible. The use of respirators as long term protection of workers is not an acceptable OSHA compliance procedure. There are several reasons for not accepting respirators as long term protection of workers. The first important reason is contained in the OSHA Act 29 U.S.C. 655 which states that OSHA as an employer "shall furnish to each of his employees employment and place of employment which are free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees". The use of long-term protection would shift the obligation of compliance from the employer to the employee.

OSHA Compliance Assessment

The OSHA regulations relating to the protection of workers health were reviewed to determine if major aspects of SWASS production were in compliance. Specifically, OSHA regulations were reviewed relating to respirators, and controls of work processes to reduce work place dispersion of air contaminants. The specific regulations and a discussion follows:

Personal Protective Equipment

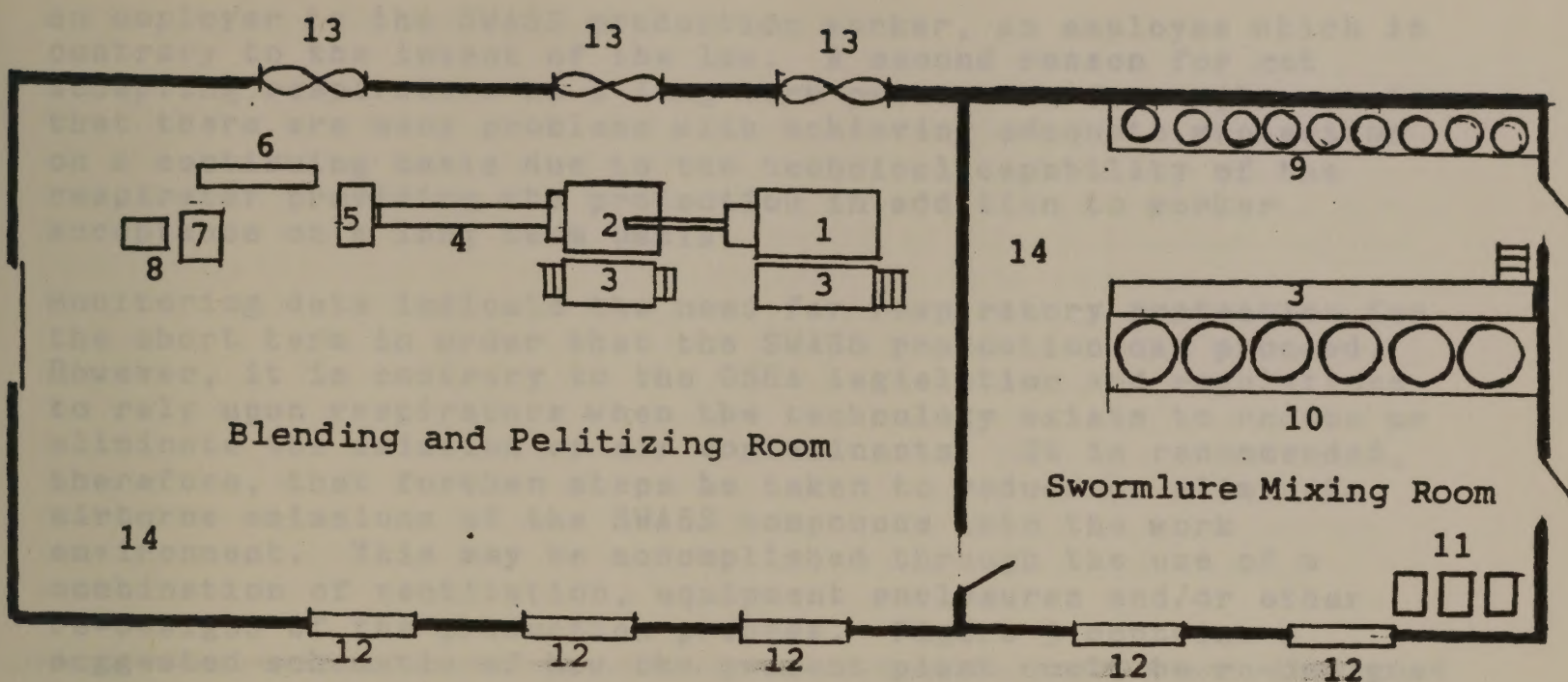
1910.134 Respiratory protection. "(a) Permissible practice. (1) In the control of those occupational diseases caused by breathing air contaminated with harmful dusts, fogs, fumes, mists, gases, smokes, sprays or vapors, the primary objective shall be to prevent atmospheric contamination. This shall be accomplished as far as feasible by accepted engineering control measures (for example, enclosures or confinement of the operation, general and local ventilation, and substitution of less toxic materials). When effective engineering control are not feasible, or while they are being instituted, appropriate respirators shall be used pursuant to the following requirements."

Toxic and Hazardous Substances

1910.1000 Air contaminants. "(e) To achieve compliance with paragraph (a) through (d) of this section (dealing with air contaminants) administrative or engineering controls must first be determined and implemented whenever feasible. When such controls are not feasible to achieve full compliance, protective equipment or any other protective measures shall be used to keep the exposure of employees to air contaminants within the limits prescribed in this section. Any equipment and/or technical measures used for this purpose must be approved for each particular use by a competent industrial hygienist or other technically qualified person. Whenever respirators are used, their use shall comply with 1910.134."

Interpretation

The two proceeding regulations simply state that if there are air contaminants in the workplace in excess of the prescribed OSHA regulations the contamination must be reduced or eliminated at its source if at all possible. The use of respirators as long term protection of workers is not an acceptable OSHA compliance procedure. There are several reasons for not accepting respirators as long term protection of workers. One most important reason is contained in the OSHA Act P.L. 91-596 which states that USDA as an employer "shall furnish to each of his employees employment and place of employment which are free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees". The use of respiratory protection would shift the obligation of compliance from USDA as



1. Blender
2. Pelletizer
3. Work Platform
4. Conveyor
5. Scale
6. Bag Sealer
7. Pallet
8. Forklift Truck
9. Ventilated 55 Gal
Drum Dispensing
Station
10. Ventilated Swormlure
Mixing Tanks
11. Wax Heaters
12. Fresh Air Intake
13. Exhaust Fans
14. Dry Storage

Suggested SWASS Production Facility
Figure 3

an employer to the SWASS production worker, an employee which is contrary to the intent of the law. A second reason for not accepting respirators as a long term protection for employees is that there are many problems with achieving adequate protection on a continuing basis due to the technical capability of the respirator providing the protection in addition to worker acceptance on a long term basis.

Monitoring data indicate the need for respiratory protection for the short term in order that the SWASS production can proceed. However, it is contrary to the OSHA legislation and regulations to rely upon respirators when the technology exists to reduce or eliminate the emission of air contaminants. It is recommended, therefore, that further steps be taken to reduce or eliminate airborne emissions of the SWASS compounds into the work environment. This may be accomplished through the use of a combination of ventilation, equipment enclosures and/or other re-designs of the production process. Figure 3 contains a suggested schematic of how the present plant could be re-designed to better control the work environment. It is suggested, however, that chemical engineers familiar with current production technology be employed to develop more definitive production layout and emission control procedures.

Toxicological Review of SWASS Ingredients

A review of the literature regarding the toxicological aspects of the SWASS ingredients was conducted to characterize the potential effect on the health of the SWASS production workers. The information obtained was reviewed in terms of its impact on the SWASS program. Therefore, some aspects of the toxicology of the SWASS ingredients may not be discussed in this report. To simplify the toxicological summary, Table 5 was prepared in addition to the discussion which follows for each SWASS chemical component. The table lists LD₅₀'s for oral administered toxicants only for the rat species for comparison purposes. The one exception is valeric acid where no oral LD₅₀ could be found. Inhalation studies had been conducted in some cases and LC₅₀ determinations are shown. An LD₅₀ or LC₅₀ is an indication of the lethal dose (LD) or lethal concentration (LC) producing mortality in 50 percent of a study population.

Many of the SWASS chemicals have work place exposure levels established either by the American Conference of Governmental Industrial Hygienists (ACGIH) or the Occupational Safety and Health Administration (OSHA). Table 5 shows these levels where applicable. In addition, work place exposure levels were proposed for three SWASS ingredients due to their potential severe adverse effect on the health of the production workers: (dimethyl disulfide, indole and valeric acid). It was recommended that the TLV for DDVP be lowered to 0.5 mg/M³ from 1.0 mg/M³ based upon the evidence found in the literature review. The relative acute toxicity for each chemical is shown in Table 5 as a quick reference. The rating system used for the determination of relative acute toxicity is common to industrial toxicology and can be found in several references. The original paper on the determination of acute toxicity classes can be found in the appendix of this report. (1)

Two questions remain unanswered after this toxicological review. One question is the combined or synergistic effect of employee exposure to these chemicals during the production process. It is not known if the chemicals will tend to enhance or reinforce each other or produce yet unknown effects. The second question is in regards to the chronic effects of the chemicals. Historically, toxicity studies have focused on acute toxicity. For example, one chemical, indole has been identified in chronic rat studies as being a leukemogen which could have the same chronic effect on humans. Acute toxicity studies did not reveal leukemia as a potential health effect due to indole exposure. It is strongly recommended therefore that an industrial toxicologist examine the information obtained in this report as well as the SWASS production facilities. The findings and recommendations of such an individual will add to the knowledge of the effects of the SWASS chemicals on the workers health, and further protections that may be required.

Acetic Acid

Acetic acid is an irritant due to acute exposure of the skin, respiratory tract and eyes with moderate to severe irritation starting at approximately 100 ppm. Other reported effects due to chronic exposure include, conjunctivitis, bronchitis, pharyngitis and erosion of teeth. Severe acute exposures of 800-1200 ppm cannot be tolerated for longer than three minutes and exposure of rats to concentrations of 16,000 ppm has killed one of six.⁽²⁾ The oral LD₅₀ in rats is 3310 mg/kg and LC₅₀ is 5620 ppm/1 hr.⁽³⁾ This would place acetic acid in the slightly toxic category.

The ACGIH TLV of 10 ppm (25 mg/m³) is recommended to prevent undue irritation. The OSHA PEL is the same.⁽⁴⁾ Only one sample of 2.4 mg/m³ has been obtained at the SWASS production plant. This sample was from the first survey. Due to the apparent low toxicity and low concentration of acetic acid no other samples were deemed necessary.

Benzoic Acid

Benzoic acid apparently would be an irritant of the eyes, skin and respiratory tract due to severe acute or chronic exposures. Benzoic acid is used as a medication as well as a food additive. Chronic low level exposure to flour treated with benzoic acid has been reported to produce allergic contact dermatitis.⁽⁶⁾ Also, human ingestion of 1 to 1.5 gm of benzoic acid has produced gastric pain, nausea and vomiting.⁽⁷⁾ The LD₅₀ of benzoic acid is 2530 mg/kg⁽³⁾ which would place it in the slightly toxic category. There has not been an ACGIH TLV or OSHA PEL established for benzoic acid. Due to its apparent low toxicity and low vapor pressure airborne concentration measurements were not made at the SWASS production plant. Personal protective equipment such as gloves and clothing appear to be adequate to prevent allergic contact dermatitis.

Butyric Acid

The toxicity of butyric acid to humans has not been reported but presumably it could be considered a respiratory and skin irritant. One study on rats produced an oral LD₅₀ of 2940 mg/kg with the same rats being able to endure prolonged exposure to a concentrated vapor inhalation with no effects. (9) The same study showed an oral LD₅₀ of 8790 mg/kg in female rats. A toxicity review of butyric acid in 1960 pointed out its irritation characteristics as well as the possible depression of the central nervous system in animals. More severe effects were noted from intravenous administration of butyric acid. (10) Accordingly, butyric acid would be considered slightly toxic. There has not been an ACGIH TLV or an OSHA PEL established for butyric acid. Due to its apparent low toxicity and low vapor pressure airborne concentration measurements were not made at the SWASS production plant. Personal protective equipment appears to be adequate to prevent skin contact.

P-Cresol

Of the three isomers of cresol, ortho, meta and para, p-cresol is considered to be the most toxic. It is a strong dermal irritant and frequently causes dermatitis. Serious or fatal poisoning may result if large skin areas are wet with cresol and not removed immediately. Total human toxicity is not known, but effects from exposure could include irritation, corrosion, hemorrhages, liver and kidney damage. (12,13) Studies on rats have shown an oral LD₅₀ of 207 mg/kg which would place it in the moderately toxic category. The ACGIH TLV of 5 ppm (22 mg/m³) is established at a level comparable to that of phenol which has similar toxicity to humans. The OSHA PEL is the same. P-cresol is a substance of low volatility and ordinarily would not present a vapor hazard to employees. The most likely exposure route would be through skin contact or the inhalation of particles with cresol adsorbed on them. One sample obtained in the batch mixing area of the plant did not reveal the presence of p-cresol and therefore the airborne exposure appears to be minimal.

0.7 mg/M³ for
12 month occupational
exposure

1.0 mg/M³ chronic dose
for 1.5 - 5.5 hours

1.0 mg/M³ for 8 hour
work day and 40 hours
per week

Erythrocyte
cholinesterase depressed
35 percent. Serum
cholinesterase depressed
60 percent.

Plasma cholinesterase
depressed 20-35
percent.

Current ACGIH TLV and
OSHA PEL with
anticipated 20 percent
reduction in plasma
cholinesterase.

Even though the above table reflects adverse health responses due to inhalation of DVP, researchers had difficulty in achieving actual concentrations in air when exposing laboratory animals. This is apparently due to the fact that DVP is readily absorbed on surfaces and hydrolyzed by moisture. DVP is also readily absorbed through unbroken skin which could be a source of intoxication more severe than that achievable through the inhalation of DVP vapors.

A review of the effects of a 35 percent depression of cholinesterase indicates a potential for weakness, headache, sweating, nausea, vomiting and pallor. There is also a report that a depression of 25 percent or more is strong evidence of excessive absorption. (11) All of the above data seems to indicate that the current (ACGIH TLV and OSHA PEL) 1.0 mg/M³ is too high to adequately protect worker's health from DVP inhalation exposure. Also, as can be seen from the above data there is no safety factor incorporated in the TLV or PEL since a

Dichlorvos (DDVP)

One of the major toxicological effects of Dichlorvos (DDVP) is the depression of blood cholinesterase. Other recognized effects include leukocytosis, neutrophilia and a decrease in lymphocytes and monocytes. Symptoms intoxication of in an increasing order of severity include weakness, headache, nausea, abdominal cramps, blurred vision, sweating, convulsions and coma. A number of human toxic responses to DDVP exposure have been reported and are summarized below.

Dose

Response

0.14 to 0.33 mg/M³ for
30 min/hr, 10 hr/day
for 14 days

No change in
cholinesterase (15)

0.3 to 0.5 mg/M³ for
8 hour work day

No effect level (15)

0.7 mg/M³ for
12 month occupational
exposure

Erythrocyte
cholinesterase depressed
35 percent. Serum
cholinesterase depressed
60 percent. (16)

1.0 mg/M³ single dose
for 1.5 - 8.5 hours

Plasma cholinesterase
depressed 20-25
percent. (15)

1.0 mg/M³ for 8 hour
work day and 40 hours
per week

Current ACGIH TLV and
OSHA PEL with
anticipated 20 percent
reduction in plasma
cholinesterase. (15, 16)

Eventhough the above table reflects adverse health response due to inhalation of DDVP, researchers had difficulty in achieving lethal concentrations in air when exposing laboratory animals. This is apparently due to the fact that DDVP is readily absorbed on surfaces and hydrolyzed by moisture. DDVP is also readily absorbed through unbroken skin which could be a source of intoxication more severe than that achievable through the inhalation of DDVP vapors.

A review of the effects of a 25 percent depression of cholinesterase indicates a potential for weakness, headache, sweating, nausea, vomiting and salivation. There is also a report that a depression (of) 25 percent or more is strong evidence of excessive absorption. (17) All of the above data seems to indicate that the current (ACGIH TLV and OSHA PEL) 1.0 mg/M³ is too high to adequately protect worker's health from DDVP inhalation exposures. Also, as can be seen from the above data there is no safety factor incorporated in the TLV or PEL since a

1.0 mg/M³ exposure is bordering on severe adverse health effects. It is strongly suggested therefore, that a permissible DDVP exposure level of 0.5 mg/M³ TWA be used for SWASS production rather than the 1.0 mg/M³.

Early measurements of the work environment for DDVP indicated that DDVP is released into the production area. Measurements of 0.98 mg/M³ to 2.44 mg/M³ were obtained near and on top of the SWASS mixers and bagging machines. Some efforts were made to enclose the production facilities by fabricating a lid for the mixer, providing an enclosed hopper and screw conveyor to the pelletizer and enclosing the bagging hopper. Subsequent personal monitoring indicate worker exposures of 0.48 mg/M³ to 2.49 mg/M³ during mixing, 0.148 mg/M³ during pelletizing and 0.166 mg/M³ to 0.234 mg/M³ during bagging. It appears therefore that better enclosures and/or increased local ventilation is needed at the mixing station. Measurements conducted on the C-45 discharging aircraft indicate one reading of 0.043 mg/M³. A new bag with a plastic liner to seal in vapors in conjunction with good cabin ventilation are apparently responsible for this low reading.

A bioassay of DDVP by the National Cancer Institute revealed that DDVP does not appear to have carcinogenic properties. (18)

Chemical	MM ⁽¹⁾	TLV/TWA ⁽²⁾ (ppm)	AE ⁽³⁾ (ppm)	CEILING ⁽⁴⁾
n-Butyl Mercaptan	90.2	OSHA 10	2500	None
C ₄ H ₁₀ S		ACGIH 0.5	2000	100
Ethyl Mercaptan	62.12	OSHA 10 ⁽³⁾	2400	100
C ₂ H ₆ S		ACGIH 0.5		
n-Propyl Mercaptan	76.12	OSHA 10 ⁽³⁾	2400	100
C ₃ H ₈ S				
Diethyl Disulfide	188.28	OSHA 10 ⁽³⁾	2400	100
C ₄ H ₁₀ S ₂				

(1) MW = Molecular Weight

(2) TLV/TWA = Threshold Limit Value/Time-Weighted Average

(3) Ceiling Value

(4) Suggested by OSHA

The ACGIH TLV's for n-Butyl Mercaptan and Ethyl Mercaptan are 10 ppm were established on the basis of preventing irritation and acute toxic effects. Suggested by OSHA.

Dimethyl Disulfide

An airborne concentration exposure level for dimethyl disulfide has not been established by either OSHA or ACGIH. The only reference to the toxicity of dimethyl disulfide was found in the NIOSH 1979 Registry of Toxic Effects of Chemical Substances⁽³⁾, which identifies Chemical Products Division, Crown Zellenbach, Camas, Washington, 98607, as the source of toxicity data through a personal communication to NIOSH. They reported an LC₅₀ of 805 ppm in rats.⁽¹⁹⁾ According to contemporary toxicity classifications, and LC₅₀ of 805 ppm for dimethyl disulfide would place it in the moderately toxic category. An earlier inhalation study demonstrated that rats exposed to concentrations of 250 ppm for thirteen six hour exposures showed lethargy, respiratory difficulty and on autopsy congested organs. Twenty six-hour exposures at 100 ppm did not reveal abnormal changes in rats.⁽²⁰⁾ Therefore, by analogy with similar compounds, and approximation of an acceptable airborne exposure level can be established.

To arrive at an approximation of an acceptable airborne exposure level by analogy, a review was conducted of the ACGIH Documentation of the Threshold Limit Values for n-Butyl Mercaptan and Ethyl Mercaptan, which have similar chemical structures and established TLV's. In addition, a review was conducted of the NIOSH Criteria for a Recommended Standard for Occupational Exposure to n-Alkane Mono Thiols⁽²¹⁾, which also have a similar chemical structures and recommended exposure limits. A summary of the comparative data is shown below along with the current OSHA Permissible Exposure Limit (PEL) for n-Butyl Mercaptan and Ethyl Mercaptan.

<u>Chemical</u>	<u>MW</u> ⁽¹⁾	<u>TLV/PEL</u> ⁽²⁾ (ppm)	<u>LC</u> (ppm)	<u>Species</u>
n-Butyl Mercaptan $C_4H_{10}S$	90.2	OSHA 10 ACGIH 0.5	2500 4020	Mouse Rat
Ethyl Mercaptan C_2H_6S	62.14	OSHA 10 ⁽³⁾ ACGIH 0.5	4420	Rat
n-Alkane Thiols	48.11	NIOSH 0.5 ⁽³⁾	28-2950	Mouse
$C_nH_{2n} + ISH$	to 110.18		33-4870	Rat
Dimethyl Disulfide $C_2H_6S_2$	94.2	USDA 1.0 ⁽⁴⁾	805	Rat

(1) MW = Molecular Weight

(2) TLV/PEL = Threshold Limit Value/Permissible Exposure Limit

(3) Ceiling Value

(4) Suggested by USDA

The ACGIH TLV's for n-Butyl Mercaptan and Ethyl Mercaptan of 0.5 ppm were established on the basis of preventing irritation rather than toxic effects. Reportedly, also, human exposures to

concentrations for several hours to 3-4 ppm did not produce toxic effects other than discomfort from the strong odor. The literature cited by ACGIH rated these two chemicals as slightly toxic.

The NIOSH Criteria for a Recommended Standard for n-Alkane Thiols indicates that the most prevalent biological effect of the thiols at high concentrations is the effect on neurons with resulting injury and possible CNS depression in addition to the obnoxious odors. It was reported that human exposures to ethanethiol (methyl mercaptan) at 4 ppm for 3 hours/day for 5 days caused olfactory fatigue and mucosal irritation. These symptoms returned to normal after removal of exposure. No significant adverse effects were found from human exposures for 20 minutes at 50 and 112 ppm. Significant signs and symptoms begin to occur at higher concentrations for longer periods of time. The NIOSH recommendation of 0.5 ppm ceiling concentration for the thiols is based upon irritation properties due to obnoxious odors as well as perceived chronic systemic effects.

Therefore, by analogy with the above information, a tentative exposure level can be determined for dimethyl disulfide to protect USDA employees during an 8-hour work day and a 40-hour work week. It is proposed that an exposure level of 1 ppm Time Weighted Average (TWA) be used for the SWASS production and dispersion operations. Also, since there is a high probability of skin absorption of dimethyl disulfide, all worker skin contact with the chemical or the finished pellets must be avoided. When additional medical or toxicological data becomes available, the exposure level can be modified accordingly.

Air sampling₃ for dimethyl disulfide indicates that concentrations of 72.8 mg/m³ (18.9 ppm) were observed downstream of the air passing through the plant and the batch mixing area. In view of the tentative permissible exposure value of 1 ppm, there is reason to believe that personal protective equipment is essential to protect employees' health, and that efforts should be made to better control dimethyl disulfide emissions. The highest concentration measured on board the aircraft was 0.1 mg/m³ (0.026 ppm) directly behind the pilot's left shoulder.

Personal breathing zone monitoring in the plant₃ revealed dimethyl disulfide concentrations ranging from 43.5 mg/m³ (11.3 ppm) on the mixing operation to 107 mg/m³ (27.8 ppm) on the pelletizer. Dimethyl disulfide has an odor threshold of approximately 2.0 ppb giving excellent warning properties far below the proposed TLV of 1.0 ppm (22). However, in the presence of other SWASS ingredients it may not be possible to distinguish it from the other chemicals.

Indole

Indole, also known as 2,3, Benzopyrrole, has not been studied for chronic human toxicity. However, a Russian study addressed acute human inhalation exposures. (24) A number of animal studies have been conducted also in relation to indole as a food additive. There is approximately 425 pounds/year of indole added to foods resulting in an estimated per capita consumption of 4.2 mg/day. Indole is naturally occurring in beer, cheese, coffee, tea, eggs, fish and grapes. It is also naturally occurring in fecal matter.

Acute animal toxicity studies reveal an oral LD_{50} in rats of 1000 mg/Kg. (25) This would place indole in the category (26) of moderate to slight acute toxicity. However, German studies (28) have demonstrated that indole is a leukemogenic agent in rats and mice when administered sub-cutaneously. A check with the National Cancer Institute, Bioassay Department revealed however, that they do not have a file on indole and are not actively investigating its leukemogenic properties.

The Russian study demonstrated that a saturated concentration of indole is on the order of magnitude of 0.01 mg/l (10 mg/M^3) (2 ppm). This would be the theoretical upper limit for possible workplace exposures. The odor threshold was found to be approximately 0.45 mg/M^3 (.09 ppm). Nausea symptomology becomes evident at 0.9 mg/M^3 . Their conclusion is that "inhaling the indole vapors in concentrations of more than 1.0 mg/M^3 may lead to negative subjective sensations: headaches, nausea". Therefore, based upon this information an 8 hour TLV₃ of 0.3 mg/M^3 (0.07 ppm) and an acute short term limit of 1.0 mg/M^3 (0.2 ppm) is proposed. It is not known if human chronic exposure to indole by inhalation will produce the leukemogenic effects found in mice and rats. The Russian study demonstrated that indole inhaled by rabbits in concentrations of 0.009 mg/l did not appear in the blood. Indole is therefore being metabolized or eliminated. It should also be kept in mind that humans are routinely exposed to inhalation of intestinal gases containing indole and therefore, the potential health hazard if any would have appeared. The potential health problems due to human cutaneous exposure is unknown, but conceivably by analogy with the demonstration of leukemia from sub-cutaneous injections in rats and mice a health risk does exist. Therefore, direct skin contact with indole must be avoided.

The potential exposures to indole during SWASS production would be during the handling of the raw chemical during formulation and mixing as well as indole attached to fugative dust particles. Protective gloves and clothing are used during mixing and therefore, this route of exposure is minimized. Air monitoring for indole attached to dust particles indicated that if it was present it was below the detection limit of 0.001 mg based upon approximately 500 liter air samples.

Isobutyl Alcohol

A thorough literature review by the Flavor and Extracts Association was conducted on indole. A summary of their findings in the literature from 1920-1977 is contained in the appendix of this report. (27)

of 8000 ppm (24,000 mg/m³) LD₅₀ of 2450 mg/kg. Isobutyl alcohol is the slightly higher (150 mg/m³) and the OSHA PEL is 100 mg/m³. Values were established for isobutyl alcohol appear to be reasonable. Batch mixing area concentrations that isobutyl alcohol was found in the process. Isobutyl alcohol was found in the dispersing aircraft. Batch mixing area concentrations of 37.5 mg/m³ activities, 80.4 mg/m³ at the loading station. The process is used for increased ventilation and process to control vapor concentrations.

Isobutyl Alcohol

No information is available regarding the human toxicity of isobutyl alcohol. Current recommended exposure levels are based upon animal studies. Inhalation studies on rats indicate an LC_{50} of 8000 ppm (24,000 mg/M^3). Ingestion toxicities indicate an LD_{50} of 2460 mg/kg. (3) These two studies would place isobutyl alcohol in the slightly toxic category. The ACGIH TLV is 50 ppm (150 mg/M^3) and the OSHA PEL is 100 ppm (300 mg/M^3). These values were established by analogy with n-butyl alcohol and appear to be reasonable. (29) Early measurements in the SWASS batch mixing area revealed a concentration of 36 mg/M^3 indicating that isobutyl alcohol was being emitted by the production process. Isobutyl alcohol was not detected on board the C-45 disbursing aircraft. More recent personnel monitoring revealed concentrations of 57.3 to 163.7 mg/M^3 at SWASS mixing work activities, 80.2 mg/M^3 at pelletizing, and 55.6 mg/M^3 at the bagging station. The readings in the mixing work area indicate a need for increased ventilation and/or enclosing the production process to control vapor emissions.

Phenol

The toxicological behavior of phenol in humans has not been precisely defined. Several inhalation studies of animals indicate involvement of the lungs, heart, liver and kidneys. However, due to the low volatility of phenol it is more likely to be a skin absorption hazard than an inhalation hazard. It is reported that humans have urinary excretions as high as 2 grams per day of phenol. This would correspond to an inhalation exposure of 50 ppm for eight hours. (31) It has been reported also that humans retain 60-88 percent of inhaled phenol which is almost completely excreted in the urine. There are numerous reports of skin exposure to phenol with a resulting injury and/or intoxication. It appears that the skin represents the primary route of absorption of phenol liquid and vapor with phenol vapors being as readily absorbed through the skin as through the lungs. Low level skin absorption of phenol vapors can apparently take place with out discomfort. (32) The current ACGIH TLV and OSHA PEL were established in 1952 at 5 ppm (19 mg/M³) and has remained at this level in the absence of evidence that it should be lower. (30) NIOSH in its recommended standard has suggested that this exposure level be retained for an 8 hour work shift. (32) Two measurements in the SWASS batch mixing area failed to reveal measurable concentrations of phenol and therefore, further measurements were not attempted. It appears that the greatest phenol hazard in SWASS production will be from solid, liquid or vapor exposure to the unprotected skin. Therefore, the continued use of protective gloves and equipment is essential to protect workers. The National Cancer Institute was not able to conclusively demonstrate carcinogenicity of phenol during ingestion studies on rats and mice. (33)

Sec-Butyl Alcohol

Human reactions resulting from chronic or acute exposures to sec-butyl alcohol have not been reported. Animal studies reflect a high LD_{50} of 2460 mg/kg and an LC_{50} of 8000 ppm for 4 hours indicating a slightly toxic substance. By analogy with similar substances, the effects of human exposure that can be expected include the defatting and irritation of the skin, and in the case of high vapor concentrations, narcosis and irritation of the eyes and upper respiratory tract. The ACGIH TLV was 150 ppm for at least ten years and in 1981 it was lowered to 100 ppm (305 mg/ M^3). (35) The current OSHA PEL is 150 ppm (450 mg/ M^3). (4) Measurements in the batch mixing area revealed a concentration of 15 mg/ M^3 indicating that sec-butyl alcohol was being evolved by the production of SWASS. Air samples obtained on board the C-45 disbursing aircraft did not reveal that sec-butyl alcohol was being released. Personal monitoring of employees in the SWASS production area revealed breathing zone concentrations of 24.3 to 68.0 mg/ M^3 at the mixing operation, 34.6 mg/ M^3 at the pelletizer, and 27.6 mg/ M^3 at the bagging machine. These readings are well below the TLV and indicate that sec-butyl alcohol is probably not a health hazard in SWASS production. It is however, easily measured and is a good indicator of the emission of SWASS ingredients into the environment. As with other SWASS chemicals, skin contact should be avoided through the use of personal protective equipment.

Therefore, by analogy, a TLV of 1 ppm (10 mg/ M^3) is proposed for valeric acid for SWASS production to avoid the irritating properties of the acid vapors. Monitoring for valeric acid has not been conducted due to its apparent low toxicity and the low measured concentrations of valeric acid. Individuals exposed to high levels of acid vapors will usually avoid exposure due to the eye and respiratory irritation. There would be a slight concern, however, of synergism between valeric acid, diisobutyl alcohol, and the alcohols in affecting the nervous system.

Valeric Acid

There is no information available on the toxic effects of valeric acid on humans. There are however, reports of central nervous system depression in rabbits and gastro-intestinal disorders and drowsiness⁽³⁷⁾. There is a suggestion, therefore, of toxicity to the central nervous system due to valeric acid exposure. Eye and skin irritation would also be expected from vapor and liquid contact. A TLV for valeric acid may be established by analogy with similar acids based upon the mouse intervenous (inv-mvs) LD₅₀, the irritation properties of acid vapors, and established TLVs. Three acids, acetic, formic and propionic were selected for this purpose and are shown below.

<u>Chemical</u>	<u>MW</u>	<u>TLV</u>	<u>LD 50 In Mice</u>
Acetic Acid $C_2H_4O_2$	60.05	10 ppm ⁽¹⁾ 25 mg/M ³	525 mg/kg
Formic Acid CH_2O_2	46.02	5 ppm ⁽¹⁾ 9 mg/M ³	145 mg/kg
Propionic Acid $C_3H_6O_2$	74.08	10 ppm ⁽¹⁾ 30 mg/M ³	625 mg/kg
Valeric Acid $C_5H_{10}O_2$	102.13	5 ppm ⁽²⁾ 20 mg/M ³	129 mg/kg

(1) ACGIH TLV

(2) USDA Proposed TLV

Therefore, by analogy, a TLV of 5 ppm (20 mg/M³) is proposed for valeric acid for SWASS production to avoid the irritating properties of the acid vapors. Monitoring for valeric acid has not been conducted due to its apparent low toxicity and the low measured concentrations of acetic acid. Individuals exposed to high levels of acid vapors will usually avoid exposures due to the eye and respiratory irritation. There would be a slight concern, however, of synergism between valeric acid, dichlorvos, and the alcohols in affecting the nervous system.

Heat Stress

The SWASS production activities are conducted under "open air" conditions with heat stress exposures ranging from direct radiant energy exposure to shade during hot humid summer days.

The ACGIH heat stress criteria is the most widely used and recognized for use in work environments. They recommend the use of the Wet Bulb-Globe Temperature Index (WBGT) for evaluating heat stress exposure. (39) The criteria is established on the basis that a worker should be able to function effectively under given conditions of temperature, humidity, radiant energy and body metabolism rate without suffering adverse health effects.

Sampling protocol for heat stress was conducted using the general procedures discussed in the NIOSH Criteria for a Recommended Standard -- Occupational Exposure to Hot Environments. The WBGT was measured using a Reuter-Stokes RSS-211A heat stress monitor which electronically determines the natural wet bulb (NWB), dry bulb (DB), and globe temperatures (GT). The WBGT is then calculated from the formula $WBGT = 0.7NWB + 0.2 \text{ GT} + 0.1 \text{ DB}$ for outdoor locations and $WBGT = 0.7 \text{ WB} + 0.3 \text{ GT}$ for indoor locations. For the purposes of determining acceptable WBGT conditions in a work environment, it is necessary to establish the work and metabolism rate of the employees.

The metabolism rate of the SWASS workers is estimated to be in the moderate range of 200-350 kilocalories per hour (kcal/hr) with lower rates during rest periods. The rate is based upon observed work activity of walking, moving 55 gallon drums, lifting buckets of swormlurg bags of pellets and SWASS ingredients as well as idle time and rest periods. The estimated metabolism rate would require a WBGT of approximately 29.4°C with a 50 percent work/rest cycle. Measurements obtained on June 14, 1982, are as follows:

<u>Measurement</u>	<u>Time of Day</u>	
	<u>Morning</u>	<u>Afternoon</u>
Wind Velocity at Mixer	4-600 fpm	6-800 + fpm
Temperature Outside	31°C	35°C
Relative Humidity	67%	50%
WBGT Inside	27°C	28°C
WBGT Outside	30°C	31°C

These were not the most severe summer time conditions that would be encountered outside in Texas. They are however, representative of what might be found. It is apparent from this data that the present work situation is at the recommended limit for heat stress considerations for a 50 percent work/rest cycle. It is also apparent that the rest periods and the air conditioned rest area is essential for the health of the workers.

The effect of exposure to conditions in excess of the WBGT of

29.4°C under the present estimated metabolism rate 200-350 kilocalories would be the storage in the body of excess heat energy and the raising of the body core temperature above a healthful level. The net result could be heat exhaustion or other problems among individuals having a low level of cardiovascular fitness. It is suggested that as part of the medical monitoring program that the cardiovascular fitness of the SWASS workers be determined. They should be allowed to rest when the heat stress conditions become excessive. During the hot summer months, profuse sweating and exhaustion were observed among some workers.

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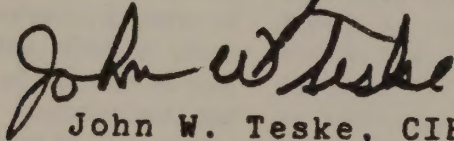
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*The numbering of the attached appendices follows the numbering of the references.

Acknowledgements

Thanks go to Lennetta Kidwell who typed the several drafts of this report and to Scott Merkle of the Safety and Health Management Division who provided helpful critiques of those drafts.

This report was prepared by:



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Senior Industrial Hygienist

Tabulation of Toxicity Classes

A Report Prepared by
HAROLD C. HODGE¹ and JAMES H. STERNER²
from Notes Taken at the Toxicological Round-Table

THE discussions of the Toxicological Round-Table during the past three years have been based on the recognized need for a healthy degree of standardization in toxicological terminology and in methods of testing. There have been several aspects of the development of this idea. One of these concerns the classification of degrees of toxicity; the current report summarizes our thinking and points out some of the needed further developments. We have taken it upon ourselves to prepare this summary for a group which included the following: H. F. SMYTH, C. P. CARPENTER, D. D. IRISH, V. K. ROWE, W. B. DEICHMANN, J. H. DRAIZE, W. F. VON OETTINGEN, C. I. BLISS, O. M. GRUHITZ, H. BRIEGER, E. A. MAYNARD, E. M. ADAMS, R. A. KEHOE, F. F. HEYROTH, L. T. FAIRHALL, L. C. MILLER, H. E. STOKINGER, A. J. LEHMAN, F. R. HOLDEN, and others.

At the A.I.H.A. meeting in April, 1947, in Buffalo, a series of terms was proposed to describe the toxicity of industrially-important chemicals. These terms were to be given a special technical significance so that—among industrial toxicologists—dosage and descriptive terms would be codified. Six ranges of toxicity beginning with the most toxic compounds might be described as follows: (1) extremely toxic, (2) highly toxic, (3) moderately toxic, (4) slightly toxic, (5) practically non-toxic, and (6) relatively harmless. To give these categories a significant reference, the probable lethal dose for man in common units of measurement are given in the accompanying table.

It is obvious that if a drop or a grain of any substance is capable of causing death, it is 'extremely toxic.' The next common unit of measurement is a teaspoonful. A substance which in this small dosage would cause death would certainly be 'highly toxic.' If an ounce were required, it seems reasonable to describe such a material as 'moderately toxic,' whereas a lethal dose of a pint

might be described as 'slightly toxic' and a quart as 'practically non-toxic.' There are relatively few materials in which a lethal dose is greater than a quart and it seems that such material could properly be designated as 'relatively harmless.' In other words, the descriptive terms logically and easily fit the amounts commonly dealt with as units of measurement. What we propose is that for various routes of administration, for example, orally, intraperitoneally, by lung, or by skin, and for specifically stated species, these common terms be defined by industrial toxicologists as referring specifically to doses effective within the defined ranges.

The industrial toxicologist has at least two problems in describing the poisonous character of chemicals handled in his plant. In the first place he must describe the toxic properties in some simple way that is understandable to other toxicologists. Since this tabulation of toxicity classes was first made a little over a year ago, it has been applied to results of toxicity testing and has been found to fill, at least for us, a long-felt need for a simple, understandable expression of the degree of toxicity. It not only has helped as a descriptive language but, in comparing the results of toxicity tests on a sizable list of compounds, these categories have materially assisted in organizing and presenting the data.

The second problem which the industrial toxicologist continuously faces is his responsibility to the plant operators and management in the translation of toxicity data into terms of 'hazard.' This translation must be in terms that will immediately and clearly describe the precautions to be used in handling the material. One very active laboratory has used the device of naming toxic substances in each hazard category so that when a new substance is investigated, it is only necessary to relate it to the few well-known materials, the handling properties of which are well-established. Since only rarely would such 'common denominator' or 'reference' compounds have

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RANGE-FINDING TOXICITY DATA

probable L. D.₅₀ value and its fiducial range are estimated by the method of Thompson⁵ using the tables of Weil.⁶ When fractional mortality is not observed, the L. D.₅₀ value is recorded without a fiducial range.

Penetration of rabbit skin is estimated by a technique essentially the one-day cuff method of Draize and associates,⁷ using groups of four male New Zealand giant albino rabbits weighing 2.5 to 3.5 kg. The fur is closely clipped over the entire trunk, and the dose, retained beneath an impervious plastic film, contacts about 1/10 of the body surface. Dosages greater than 20 ml. per kilogram of body weight cannot be retained in contact with the skin. After 24 hours' contact the film is removed, and mortality is considered complete after 14 additional days.

Earlier papers in this series ‡ have spoken of saturated vapor inhalation. Recent reexamination of our methods indicates that a less definite term is desirable. Accordingly, we now speak of concentrated vapor inhalation. This consists in exposing groups of six male albino rats to a flowing stream of air approaching saturation with vapors. The stream is prepared by passing dried air through a fritted disc gas washing bottle initially at room temperature. When carbon dioxide will react with the sample, the air stream is freed of that gas. Inhalations are continued for periods of time in an essentially logarithmic series with a ratio of two, extending to eight hours, until the period killing half the rats within 14 days of inhalation is defined. The Table records the longest period which allowed all rats to survive 14 days or, in a few instances marked by a symbol, the shortest period tried when this killed all rats.

Inhalation of known vapor concentrations by rats is conducted with flowing streams of vapors prepared by various styles of proportioning pumps. Nominal concentrations are recorded, not confirmed by analytical methods. Exposures are four hours long, although rarely an eight-hour period is used. Concentrations are in an essentially logarithmic series with a factor of two, and the Table records the concentration yielding fractional mortality among six rats within 14 days. Where no fractional mortality was observed, both the concentration yielding no mortality and that yielding complete mortality are indicated.

Primary skin irritation on rabbits records in a 10-grade ordinal series the severest reaction on the clipped skin of any of five albino rabbits within 24 hours of application of 0.01 ml. of undiluted sample or of dilutions in water, propylene glycol, or kerosene. Grade 1 in the Table indicates the least visible capillary injection from undiluted chemical. Grade 6 indicates necrosis when undiluted, and Grade 10 indicates necrosis from a 0.01% solution.

Eye injury in rabbits records the degree of corneal necrosis from various volumes and concentrations of chemical, as detailed by Carpenter and Smyth.⁸ Grade 1 in the Table indicates at most a very small area of necrosis resulting from 0.5 ml. of undiluted chemical in the eye; Grade 5 indicates a so-called severe burn from 0.005 ml., and Grade 10 indicates a severe burn from 0.5 ml. of a 1% solution in water or propylene glycol.

‡ References 1 to 4.

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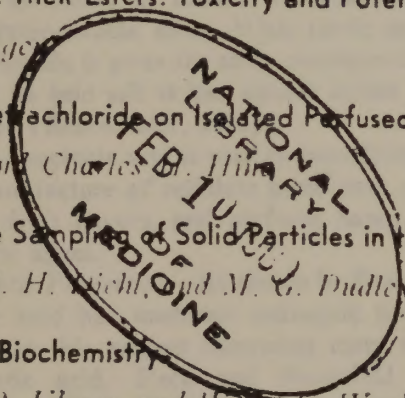
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The Aliphatic Acids and Their Esters: Toxicity and Potential Dangers.

The Saturated Monobasic Acids and Their Esters:

Aliphatic Acids with Three to Eighteen Carbons and Their Esters

W. F. von OETTINGEN, M.D., Ph.D., Bethesda, Md.

Propionic Acid

Chemistry.—Propionic acid, propanoic acid, $\text{CH}_3\text{CH}_2\text{COOH}$, has the molecular weight 74.08. It is a colorless liquid of pungent odor; has the specific gravity 0.993 at 20/4 C, the melting point -20.8°C , and boiling point 141.4°C . It is miscible with water, alcohol, and ether, and, in contrast to the lower homologues, it may be salted out from its aqueous solutions by means of calcium chloride and other readily water-soluble salts. With ferric salts and arsenic trioxide it gives the same reactions as acetic acid, and its lead salt is less soluble in hot than in cold water (Rosenthaler, 1923).

Uses.—Propionic acid is used as esterifying agent, in the manufacture of cellulose propionate, of ester solvents, fruit flavors, and perfume bases, and as fungistatic agent.

Antiseptic Properties.—As shown by Bach (1932) propionic acid has moderate antiseptic properties, and it is in this respect somewhat more effective than acetic acid. Peck and Rosenfeld (1938) showed that it has fungistatic properties down to concentrations of 0.004 mol per liter, and that it is in this respect somewhat superior to acetic acid but inferior to the higher homologues with straight carbon chains. Miller (1939) studied the retarding effect of its sodium and calcium salts on molds in dairy products; and Keeney (1943) found that 1.25% solutions adjusted to pH 5.5 had fungistatic properties for *Trychophyllum purpureum*, *Epidermophyton inguinale*, *Microsporum audouinii*, *Candida albicans*, *Aspergillus fumigatus*, and *Aspergillus flavus*, that one-tenth this concentration (0.125%) prevented the growth of *Trychophyllum gypsum*, *Trychophyllum violaceum*, *Epidermophyton rubrum*, *Epidermophyton interdigitale*, *Trychophyllum schoenleinii*, and *Microsporum lanosum*, and that 0.0125% solutions prevented the growth of *Blastomyces dermatitidis*.

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National Institute of Arthritis and Metabolic Diseases; National Institutes of Health; Department of Health, Education, and Welfare; U.S. Public Health Service, Bethesda, Md.

Clinical studies on the efficacy against various fungus infections were published by Keeney and Broyles (1943).

Irritant Action.—Propionic acid causes moderate irritation of the human skin. As shown by Oettel (1936), its contact with the human skin for 40 minutes caused distinct burning pain, erythema, and hyperemia, but less marked than that observed with acetic acid. This was followed by moderate erythema and pigmentation, and very moderate necroses.

Absorption, Fate and Excretion.—Propionic acid is readily absorbed from the gastrointestinal tract. There is no evidence that it is absorbed through the intact human skin, and in view of its high boiling point its absorption through the lungs appears quite remote. As shown by Blum (1940), and MacKay, Wick and Barnum (1940), it is not oxidized with the formation of ketone bodies by rabbits with adequate amounts of glycogen in the liver. As shown by Ringer (1912), and Rittenberg, Schoenheimer and Evans (1937), it is largely converted to glucose in phlorizinized animals, and according to Buchanan, Hastings and Nesbitt (1943) it is partly converted to glycogen in fasted rats, in contrast to acetic acid. It appears to be not excreted as such in the urine, because, as shown by Hermann and associates (1938), it is decomposed in the intestine by bacterial destruction.

Toxicity for Laboratory Animals.—Propionic acid is comparatively little toxic. According to Mayer (1886) the intravenous injection of 2.2 gm. per kilogram, given as 14% solution, causes in rabbits marked

dyspnea, increased cardiac action, pareses, and frequent urination, followed by recovery within 24 hours. Similar effects, although less severe, were seen in dogs after intravenous injection of 0.55 gm/kg. (given as 10% solution), and in cats after subcutaneous injection of 1 gm/kg., given as 10% solution. As shown by Fodera (1894) the injection of 2 cc. of a 5% neutralized solution of propionic acid, corresponding to 0.1 gm., causes in frogs fibrillary twitchings and pareses, lasting about 24 hours. As reported by Hermann (1930) the intravenous injection of 0.37 gm. (given as N/2 solution) causes in dogs a distinct, although temporary, fall of the blood pressure.

Toxicity for Man.—There are no reports on toxic effects of propionic acid in man, and dangers and hazards from this material appear quite remote.

Aliphatic Esters of Propionic Acid

Table 1 gives a synopsis of the physical-chemical properties of the five lowest aliphatic esters of propionic acid.* It shows that their specific gravity and solubility in water decrease with their molecular weight, and that their boiling points and flash points move in the opposite direction.

It also gives a partial list of the compounds for which these esters are used as solvents, and it illustrates their extensive use. In spite of this, none of these compounds have been studied toxicologically in detail.

Treon and associates (1949) determined the minimal lethal dose for methyl propionate with oral administration to rabbits as 2.55 to 3.2 gm/kg., and found that such doses cause ataxia, prostration, labored, gasping respiration, and marked hyperthermia. For ethyl propionate they gave the minimal lethal oral dose as 3.2 to 3.95 gm/kg., the symptoms being the same as reported with the lower homologue. As shown by Vogel (1897) the oral administration of 0.6 and 1.0 cc/kg. causes in rabbits stimulation of the respiratory volume. According to Fühner and Neubauer

(1907) the in vitro hemolytic action of the propionic acid esters increases with the molecular weight from methyl over ethyl to propyl propionate, the minimum effective concentrations being 0.34, 0.17, and 0.06 mol per liter, respectively.

There are no reports on the toxic effects of these esters for man, and, in view of their relatively high vapor pressure, to the effects from the inhalation of their vapors seem to be quite remote.

An ether-ester of propionic acid which has been studied toxicologically is ethyl- β -ethoxy propionate, ethoxypropionic acid ethyl ester, $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$, which has the molecular weight 146, specific gravity 0.948 at 25/25 C, and boils at 165-172 C (Scheffan and Jacobs, 1953). According to Smyth, Carpenter and Weil (1954) it is very little toxic, the oral LD_{50} for rats being 5.0 gm/kg., and that with cutaneous application to rabbits about 10 cc/kg. Its contact with the skin causes a minimum degree of irritation, and when instilled into the eye it causes some irritation.

Butyric Acid

Chemistry.—Butyric acid, butanoic acid, $\text{C}_4\text{H}_8\text{O}_2$, $\text{CH}_3\text{CH}_2\text{COOH}$, is a colorless liquid of the molecular weight 88.10 and the specific gravity 0.95 at 20/4 C, which melts at -5.5°C , boils at 164°C and which is miscible with water, alcohol, and ether. Its flash point is 170°F (76.67°C) (closed cup method). It may be salted out from its aqueous solutions by means of calcium chloride. The sodium salt differs from that of propionic acid by its great solubility in amyl alcohol. When heated with sulfuric acid and methanol, or with potassium ethyl sulfate, a pineapple-like odor is formed (Rosenthaler, 1923).

Antiseptic Properties.—As shown by Pech (1932) butyric acid has antiseptic properties which are more marked than those of propionic acid. Similarly, Peck and Rosenfeld (1938) found that its fungistatic action for *Trychophyton gypsum* is greater than that of the lower homologues, the minimum concentration being 0.00113 mol per liter (0.01%), as compared with 0.00405 mol per liter and 0.00498 mol per liter for propionic acid and acetic acid, respectively.

Irritant Action.—The irritant action of butyric acid is less marked than that of propionic acid. According to Oettel (1936)

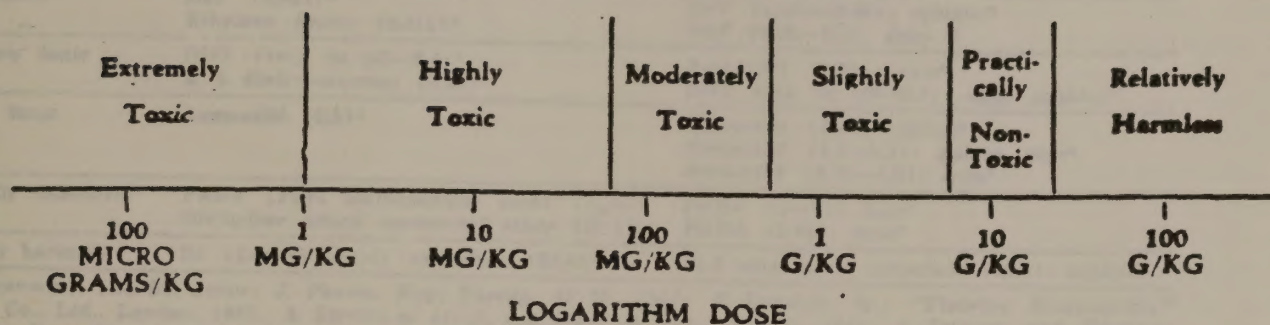
TOXICITY OF

the application followed only moderate burn emia are hard within 24 hours epidermis.

Absorption, butyric acid is absorbed in the intestinal tract, but it may have apparently different fate in the metabolism that its oral administration results occasionally in a hypoglycemic injection regular acetacetic acid, and less marked in Blum (1910) cutaneous injection in the excretion of acetoacetic acid butyric acid secondarily from (1913) found in the urine of injection of butyric acid (1944) showed injection to rats, and butyric acid is Experiments of and Evans (1944) takes place in the liver experiments with Salomon, and and Engel (1944) with liver slices by Leloir and reports of Cia (1943) it appears oxidative process in the kidneys. Buchanan, Ha with rats show butyric acid with content of the liver

Toxicity of Butyric acid central nervous system of frogs by Fod von Oettingen

GRAPH OF TOXICITY CLASSES



sufficient familiarity from industry to industry, we would suggest that the typical substances—if selected to represent handling properties—should be so simple and so widely available that each laboratory and plant could recognize the special properties of these substances without extensive investigation. For the purpose of this discussion, we wish to disregard the categories of 'hazard' and to restrict attention solely to those of 'toxicity.'

The selection of the exact numerical dosage in mg/kg which defines the ranges corresponding to the terms are arbitrarily chosen. There probably would be as many ranges as people who would select them. In the accompanying figure, the ranges are plotted graphically on a logarithmic scale and it can readily be seen that the various categories, while differing somewhat, are surprisingly comparable in length. This reasonably regular division of the logarithmic range coupled with the fact that the probable lethal dose for man, progressing from a drop or grain to more than a quart, is the approximate mid point of each division, would seem to us a practical division of the toxicity scale. See text table.

At the A.I.H.A. meeting in Boston in April, 1948, the tabulation was discussed

briefly and the need for a compilation of information already available in the literature was clearly indicated. During the past year, DR. ROBIN RANKOW has been collecting specific data in a literature survey; the accompanying tables have been prepared by him. These are offered, not as ideal examples, but as the best at hand. They are offered in the hope that these tabulations will provide the opportunity for better type substances to be suggested.

The table on oral administration gives the LD_{50} doses for rats in g/kg. Sodium fluoracetate was the best example of an extremely toxic substance. In fact, very few substances were found of which less than a mg/kg was rapidly fatal. The highly toxic substances, sodium fluoride and ethylene imine, are believed to be widely known as are most of the examples given in the other categories. Comparative data from a few other species are included.

The same terms have been applied to the description of intraperitoneal administration, with, however, a shift of dosage toward smaller values by a factor of 2 to 10 (or approximately one class unit). This relationship was chosen arbitrarily on the basis of limited data and may well need revision when more evidence is accumulated.

The compounds listed in the table covering lethal effects after intraperitoneal administration are duplicates, in some cases, of those in the oral toxicity table. This was felt to be a desirable feature. The exact toxicity of aminopterin in rats is a needed figure. The highly toxic nitrogen mustards were selected as the type substances for this category and it is interesting to note that mustard gas and di-isopropyl fluorophosphate, two of the moderately toxic substances, are also chemical warfare agents. The other compounds listed are, in

TEXT TABLE

Toxicity Rating	Category	Single Oral Dose	Probable Lethal Dose for Man
1	Extremely toxic	1 mg or less/kg	A taste 1 grain
2	Highly toxic	1—50 mg	1 tsp. 4 cc
3	Moderately toxic	50—500 mg	1 oz. 30 g
4	Slightly toxic	0.5—5 g	1 pint 250 g
5	Practically non-toxic	5—15 g	1 quart
6	Relatively harmless	15 g and more	> 1 quart

ORAL ADMINISTRATION (GM/KG)

Category	Rats	Other Species
Extremely toxic	Sodium fluoroacetate (0.0001) ¹	Sodium fluoroacetate (50 µg); dogs ¹⁰
Highly toxic	NaF (0.047) ²	NaF (0.023—0.90); rabbits ¹²
	Ethylene imine (0.015) ³	NaF (0.05—0.1); dogs ¹¹
Moderately toxic	DDT (10% in oil—0.3) ⁴	Acetanilid (0.25); cats ⁹
	4, 6 dinitro-o-cresol (0.05) ⁵	DDT (5% in oil—0.3); cats, rabbits ¹²
Slightly toxic	Acetanilid (0.3) ⁶	Acetanilid (1.5); rabbits ⁹
		Acetanilid (1.4—1.5); guinea pigs ⁹
		Acetanilid (0.75—1.0); dogs ⁹
Practically non-toxic	PABA (Para aminobenzoic acid) (>6) ¹	PABA (1—3); dogs ⁹
	Diethylene glycol monoethyl ether (30.6) ⁷	PABA (2.85); mice ⁹
Relatively harmless	Di (2-ethyl hexyl) phthalate (30.6) ⁸	Di-2 ethyl hexyl phthalate (33.9); rabbits ⁹

1. CHENOWETH and ST. JOHN: *J. Pharm. Exp. Therap.*, 89:76, 1947. 2. ROHOLM, K.: "Fluorine Intoxication." Lewis & Co., Ltd., London, 1937. 3. SMYTH et al: *J. Ind. Hyg. & Tox.*, 23:259, 1941. 4. PHILLIPS and GILMAN: *J. Pharm. Exp. Therap.*, 86:87, March, 1946. 5. SPENCER et al: *J. Ind. Hyg. & Tox.*, 30:10, 1948. 6. MUMF. PRATT and PHILLIPS: *J. Am. Pharm. Assn.*, 30:91, 1941. 7. HANZLIK, P. J., et al: *J. Ind. Hyg. & Tox.*, 29:190, 1947. 8. SCOTT et al: *Proc. Soc. Exp. Biol. & Med.*, 49:184, 1942. 9. SHAFER et al: *J. Ind. Hyg. & Tox.*, 27:130, 1945. 10. CHENOWETH and ST. JOHN: op. cit. 11. LEAKE, C. D.: *J. Pharm.*, 33:279, 1928.

INTRAPERITONEAL ADMINISTRATION (GM/KG)

Category	Rats	Other Species
Extremely toxic	Aminopterin	
Highly toxic	Nitrogen mustards (0.0005—0.001) ¹²	Nitrogen mustards (0.001—0.002); mice, rabbits ¹²
Moderately toxic	NaF (0.013—0.016) ¹	NaF (0.23—0.045); dogs, rabbits ¹
	Mustard gas (0.003) ¹⁷	Mustard gas (0.006—0.008); mice, rabbits ¹⁷
	Di-isopropyl fluorophosphate (0.0002) ¹⁸	Di-isopropyl fluorophosphate (0.0004—0.003); monkeys, mice, rabbits, cats, dogs ¹⁸
Slightly toxic	Ethylene chlorohydrin (0.05—0.06) ³	Diethyl phthalate (1.V., 0.1); rabbits ¹
	Methyl bromide (0.12—0.28) ⁶	Phthalic acid (0.55); mice ¹⁰
	BAL (0.105) ¹²	BAL (0.1); mice ¹⁴
Practically non-toxic	Acetaldehyde (0.5) ²	Choline (0.32); mice ¹
	Choline (0.20—0.34) ²	PABA (1.V., 2.0); rabbits ¹²
	PABA (P-aminobenzoic acid) (4.0) ¹¹	
Relatively harmless	Diethyl phthalate (30.7) ⁷	Diethyl hexyl phthalate (128); mice ⁹

1. ROHOLM: "Fluorine Intoxication." Lewis & Co., Ltd., London, 1937, p. 16. 2. STOTZ, WESTERFELD, and BERG: *J. Biol. Chem.*, 152:41, 1944. 3. HODGE: *Proc. Soc. Exp. Biol. & Med.*, 57:26, 1944. 4. HODGE and GOLDSTEIN: *Proc. Soc. Exp. Biol. & Med.*, 51:281, 1942. 5. GOLDBLATT: *Brit. J. Ind. Med.*, 1:213, 1944. 6. MILLAR and HAGGARD: *J. Ind. Hyg. & Tox.*, 25:423, 1943. 7. SHAFER, CARPENTER, and SMYTH: *J. Ind. Hyg. & Tox.*, 27:130, 1945. 8. FLURY and WIRTH: *Arch. Gewerbepath.*, 5:1, 1933. 9. HODGE, H. C.: *Proc. Soc. Exp. Biol. & Med.*, 53:20, 1943. 10. HODGE et al: *Proc. Soc. Exp. Biol. & Med.*, 49:471, 1942. 11. RICHARDS: *Fed. Proc.*, 2:71, 1942. 12. ANGSTEN and HADER: *Science*, 101:591, 1942. 13. WATERS and STOKK: *Science*, 102:601, 1915. 14. GRAHAM and HODGE: *Brit. J. Pharm. & Chemother.*, 3:84, 1948. 15. ANKLOW et al: *J. Pharm. & Exp. Therap.*, 91:224, 1947. 16. HORTON et al: *J. Pharm. & Exp. Therap.*, 87:414, 1947. 17. KARNOVSKY et al: *J. Pharm. & Exp. Therap.*, 93:1, 1948.

INHALATION — 4-HOUR VAPOR EXPOSURE (Original Classes by H. F. Smyth & colleagues)

Category	Rats	Other Species
Extremely toxic	Ethylene imine (25—100 p.p.m.) ²	Ethylene imine (10+ p.p.m.); guinea pigs ⁹
Highly toxic	Phosgene (50—500 p.p.m.) ⁴	Nitrogen oxides (30—1000 p.p.m.); mice, guinea pigs, rabbits, cats ²
	Nitrogen oxides (30—1000 p.p.m.) ²	
Moderately toxic	Vinyl cyanide (153 p.p.m.) ²	Vinyl cyanide (153 p.p.m.); guinea pigs, rats, monkeys, dogs ³
	HCN (200—480 p.p.m.) ⁷	
	SO ₂ (400—3000 p.p.m.) ⁷	
	Methyl bromide (about 500 p.p.m.)	
Slightly toxic	Ethylene dichloride (1, 2 dichloroethane) (3000 p.p.m.) ¹	Ethylene dichloride (3000 p.p.m.); rabbits, guinea pigs, mice ¹
Practically non-toxic	Acetone (40,000 p.p.m.) ¹⁰	Isopropyl benzene (2000 p.p.m.); mice ¹
Relatively harmless	Freon	Acetone (20,600 p.p.m.); mice ⁹

1. HEPPEL et al: *J. Pharm. Exp. Therap.*, 84:53, 1945. 2. LA TOWNKY, MACQUIDDY, and TOLLMAN: *J. Ind. Hyg. & Tox.*, 23:129, 1941. 3. DUDLEY, SWENNEY and MILLER: *J. Ind. Hyg. & Tox.*, 21:255, 1942. 4. WERNER, DUNN, and von OTTINGEN: *J. Ind. Hyg. & Tox.*, 26:264, 1944. 5. SAYERS et al: U.S.P.H.S. Bull. No. 185, 1929. 6. U. S. War Department, Medical Dept., U.S.A. (Vol. XIV), "Medical Aspects of Gas Warfare," 1926. 7. SAYERS, DALLA VALLE, and YANT: *Ind. Eng. Chem.*, 26:1251, 1934. 8. FRIEDNER, KATZ, and KINNEY: U. S. Bur. Mines, Techn. Papers, 272, 1921. 9. CARPENTER, SMYTH, and SHAFER: *J. Ind. Hyg. & Tox.*, 30:2, 1948. 10. HAGGARD, GREENBERG, and TURNER: *J. Ind. Hyg. & Tox.*, 26:133, 1944.

general, fairly simple compounds. Data on some species other than rats are included.

The acute toxic response to a four-hour vapor exposure has been used by Smyth and colleagues as a standard range-finding test. The accompanying table based on their original categories lists several possible examples of toxicity categories following the inhalation of compounds ranging from the extremely toxic ethylene imine to the practically non-toxic acetone or the relatively harmless freon. Specific information about the toxicity of freon is needed. As before, data on other species than rats are given.

The original intention had been to prepare a table with similar categories in which human fatalities could be listed. This has turned out to be a forlorn hope; consequently, the accompanying table lists, instead, some human fatalities following oral exposure in which the dose appears to have been fairly well known. If this tabulation does nothing more than direct attention to the paucity of information on this important point, it will have been well worth assembling. Physicians and toxicologists should record fatalities in the current literature when doses are known.

SKIN APPLICATION (RABBITS)
(Table prepared by Henry F. Smyth, Jr., Charles P. Carpenter and Carrol S. Weil)

Extremely toxic	1 mg or less/kg	No examples
Highly toxic	1-50 mg/kg	TEPP (Tetraethyl pyrophosphate)
Moderately toxic	50-500 mg/kg	Ethylene chlorhydrin, allyl alcohol
Slightly toxic	0.5-5 g/kg	Methyl acrylate, methyl celkmoive
Practically non-toxic	5-15 g/kg	CCl ₄ , dioxane, ethylene dichloride
Relatively harmless	15 g/kg	Di-2-ethyl hexyl phthalate, dimethyl phthalate, propylene glycol

SOME HUMAN FATALITIES FOLLOWING ORAL INGESTION

Compound	Dose (gm/kg)	Total Ingestion (gm)	Reference
Mercuric chloride	0.001-0.002		DUNHAM: <i>Proc. Soc. Exp. Biol. & Med.</i> , 50:274, 1942.
Iodine	0.004-0.015	2-3	DUNHAM, op. cit.
Iodine			SOLLMAN, T.: "A Manual of Pharmacology," 1942, p. 958.
Acetanilide	0.006-0.250		MUNCH, PRATT, and PHILLIPS: <i>J. Am. Pharm. Assn.</i> , 30:91, 1941.
Phenol	0.07-0.14		DUNHAM, op. cit.
Phenol		125 (+ 31 g. camphor)	MILLER: <i>Canad. M.A.J.</i> , 46:615, 1942.
Sodium salicylate	0.7		RYDER, SHAVER, and FERRIN: <i>New Eng. J. Med.</i> , 232:716, 1945.
NaF	0.006-0.008	0.7-1.0	ROTHOLM: "Fluorine Intoxication," 1937:12.
DDT		120 cc. 5% soln.	SMITH: <i>J.A.M.A.</i> , 136:469, 1948.
DDT		30 cc. 5% soln.	(infant) HILL and ROBINSON: <i>Brit. M. J.</i> , 2:845, 1945.
Aminophylline		0.6	CABURY: <i>J.A.M.A.</i> , 70:19, 1948.
Aminophylline		1.0	CABURY: op. cit.
Seconal		0.9	WHELOCK and FREDEMAN: <i>J.A.M.A.</i> , 129:130, 1948.
Nicotine		2.0 (tobacco)	SOLLMAN, T.: op. cit., p. 403.
Nicotine		0.06 (nicotine)	SOLLMAN, T.: op. cit., p. 403.
Sodium nitrite		2.3	MANBY: <i>Analyst</i> , 70:50, 1945.
Sodium benzoate		6.0	KINNEY and WRIGHT: <i>J. Lab. & Clin. Med.</i> , 29:144, 1944.
Potassium thiocyanate		15.0	NICHOLS: <i>Am. J. Med. Sci.</i> , 170:735, 1925.
Aspirin		10-30	Editorial: <i>New Orleans M. & S. J.</i> , 98:179, 1945.
Aspirin		50	CHARTERS: <i>Brit. M. J.</i> , 1:10, 1944.
Aspirin		81	HOPKINS: <i>Lancet</i> , 248:145, 1945.
Hydroquinone and mono methyl para aminophenol sulfate		15 (73 hrs.) 15 (92 hrs.)	ZRIDMAN and DEUTL: <i>Am. J. Med. Sci.</i> , 210:328, 1945.
			ZRIDMAN and DEUTL: <i>Am. J. Med. Sci.</i> , 210:328, 1945.
Lead	5.0	20-50	CANTAROW and TRUMPER: "Lead Poisoning," Baltimore, 1944, p. 95.
Methyl alcohol		120-140	CHAMBOU: <i>Lyon Pharm.</i> , June, 1942.

MATERIAL SAFETY DATA SHEET

ACETIC ACID

CH3COOH

TLV, 10 ppm ($\approx$ 25 mg/m³)

STEL, 15 ppm ($\approx$ 37 mg/m³)

Acetic acid is a clear, colorless liquid with a pungent odor. It has a specific gravity of 1.0492 at 20° C; molecular weight of 60; a boiling point of 188° C (765 mm) 80° C (202 mm); a melting point of 16.63° C, an open cup flash point of 110° F, a refractive index of 1.3716 (20° C) and a vapor pressure of 11 mm Hg at 20° C. It is miscible with water, alcohol, glycerin and ether; insoluble in carbon disulfide.

It is used in the manufacture of acetic anhydride, cellulose acetate and vinyl acetate monomer, acetic esters, chloroacetic acid. It is also used in the production of plastics, pharmaceuticals, dyes, insecticides, photographic chemicals, food additive (as vinegar), natural latex coagulant and in textile printing.

Stern⁽¹⁾ concluded that 10 ppm is relatively nonirritating on the basis of industrial experience. Patty⁽²⁾ reported that 800-1200 ppm cannot be tolerated for longer than three minutes. Smyth⁽³⁾ found inhalation of 16,000 ppm by rats killed one of six. Vigliani and Zurlo⁽⁴⁾ regard 20 to 30 ppm to be without danger. They reported that workers exposed for 7 to 12 years at concentrations of 60 ppm, plus

one hour daily at 100 to 260 ppm, had no injury except slight irritation of the respiratory tract, stomach and skin. However, Parmeggiani and Sassi⁽⁵⁾ found conjunctivitis, bronchitis, pharyngitis and erosion of exposed teeth, apparently in the same workers. Baldi⁽⁶⁾ reported conjunctival irritation from concentrations below 10 ppm. Amdur⁽⁷⁾ found minor changes in respiration in guinea pigs inhaling 5 ppm acetic acid, with more pronounced effects at 100 ppm.

A TLV of 10 ppm and a STEL of 15 ppm are recommended to prevent undue irritation.

Other recommendations: Cook (1945) and Elkins (1959) recommended 10 ppm. The Soviet limit (1966) was 2 ppm.

References:

1. Stern, J.H.: *Ind. Med.* 12:518 (1943).
2. Patty, F.A.: *Industrial Hygiene & Toxicology*, Vol. II, p. 886, Interscience, NY (1949).
3. Smyth, H.F. Jr.: *Am. Ind. Hyg. Assoc. Q.* 17:143 (1956).
4. Vigliani, E.C., Zurlo, N.: *Arch. Gewerbepath. Gewerbehyg.* 13: 528-535 (1955). Abstr. in *Arch. Ind. Health* 13:403 (1956).
5. Parmeggiani, L., Sassi, C.: *Med. lavoro* 45:319 (1954). Cited in Patty, F.A., *Industrial Hygiene & Toxicology*, 2nd ed., p. 1779, Interscience, NY (1963).
6. Baldi, G.: *Med. lavoro* 44:403 (1953). Abstr. in *Arch. Ind. Hyg. & Occup. Med.* 9:349 (1954).
7. Amdur, M.: *Am. Ind. Hyg. Assoc. J.* 22:1 (1961).



MATERIAL SAFETY DATA SHEET

CP 2079-1F (8-79)

SECTION I

PRODUCT NAME: Glacial Acetic Acid and Reagent Grade Acetic Acid	SIZE: —
CHEMICAL NAME: Acetic Acid	CAS No. 64-19-7
FORMULA: CH ₃ COOH	
MANUFACTURER: Marketed by Eastman Chemical Products, Inc.	
ADDRESS: Kingsport, Tennessee 37662	
FOR INFORMATION ON HEALTH HAZARDS CALL: Monday thru Friday, 8 a.m.-5 p.m. (Eastern), (615) 247-0411, Ext. 3613; all other times (615) 247-0411, Ext. 4666	
FOR OTHER INFORMATION CALL: Same number as above Extension 5114	INFORMATION EFFECTIVE AS OF: January 1981

SECTION II HAZARDOUS INGREDIENTS OF MIXTURES

PRINCIPAL HAZARDOUS COMPONENT (S)	%	TLV (Units)
Not applicable.		

SECTION III PHYSICAL DATA

BOILING POINT (°F.)	245 (118.3°C)	SPECIFIC GRAVITY (H ₂ O = 1)	1.048-1.053 (20°/20°C)
VAPOR PRESSURE (mm Hg.)	11.4 mm @ 20°C	PERCENT VOLATILE BY VOLUME (%)	Virtually 100%
VAPOR DENSITY (AIR = 1)	2.07	EVAPORATION RATE (_____ = 1)	Not determined.
SOLUBILITY IN WATER	Complete.		
APPEARANCE AND ODOR	Colorless liquid, pungent odor.		

SECTION IV FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (Method used)	103°F (TCC)	FLAMMABLE LIMITS	Lel	Uel
			6.6%	19.3%
EXTINGUISHING MEDIA	Foam, Water spray, Dry chemical, CO ₂			
SPECIAL FIRE FIGHTING PROCEDURES	Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.			
UNUSUAL FIRE AND EXPLOSION HAZARDS	None known to Eastman.			

SECTION V HEALTH HAZARD DATA**HOLD LIMIT VALUE**

TWA: 10 ppm, STEL: 15 ppm, ACGIH 1979

SIGNS OF OVEREXPOSURE

Liquid causes severe skin and eye burns.
Vapor is irritating to eyes, nose, and throat.

FIRST AID MEASURES

Eye contact: immediately flush eyes with plenty of water for at least 15 minutes and get medical attention.
Skin contact: immediately flush with plenty of water for at least 15 minutes while removing contaminated clothing and shoes and get medical attention.
Vapor irritation of eyes, nose, and throat: remove from exposure, treat symptomatically, and get medical attention if symptoms persist.

SECTION VI REACTIVITY DATA**REACTIVITY**

UNSTABLE

STABLE

X

CONDITIONS TO AVOID

Not applicable.

COMPATIBILITY

(materials to avoid)

Oxidizing materials can cause a reaction.

COMBUSTIBILITY

COMPOSITION PRODUCTS

As with any other organic material, combustion will produce carbon dioxide and probably carbon monoxide.

COMBUSTIBILITY POLYMERIZATION

Occur

Will Not Occur

X

CONDITIONS TO AVOID

Not applicable.

SECTION VII SPILL OR LEAK PROCEDURES**ACTION TO BE TAKEN
IF MATERIAL IS
SPILLED OR SPILLED**

Eliminate all ignition sources.
Flush spill away with water spray. Small spills may be collected with absorbent material. Neutralize spill and/or washings with soda ash or lime.

DISPOSAL METHOD

Incineration.
Observe all Federal, state, and local laws concerning health and environment.

SECTION VIII SPECIAL PROTECTION INFORMATION**RESPIRATORY PROTECTION
(by type)**

An appropriate NIOSH-approved respirator for organic vapor (and mists, if needed) should be worn if needed.

PROTECTION

LOCAL EXHAUST

Recommended.

MECHANICAL (general)

Recommended.

SPECIAL

None known to Eastman.

OTHER

None known to Eastman.

PROTECTIVE GLOVES

Should be worn.

EYE PROTECTION

Full face respirator for vapor and mist protection if needed; otherwise, safety glasses should be worn.

**SKIN PROTECTIVE
MEASURES**

As needed to prevent skin contact.
Eye bath and safety shower.

SECTION IX SPECIAL PRECAUTIONS**ACTIONS TO BE TAKEN
DURING HANDLING AND STORING**

Material is classified as a Combustible Liquid. Keep away from heat and open flame. Keep container closed. Do not get in eyes, on skin, or on clothing. Avoid breathing vapor. Use respirator in mists. Wash thoroughly after handling.

ADDITIONAL PRECAUTIONS

Product residue may remain on or in "empty" package. All precautions for handling the product must be used in handling the "empty" package and residue. Clean before reusing or altering package. Wash contaminated clothing before reuse. Maintain workroom air concentrations below the specified TLVs. (See Section V)

Information contained herein is furnished without warranty of any kind. Employers should use this information only as a supplement to other information gathered by them and must make independent determinations of suitability and completeness of information from all sources to assure proper use of these materials and the safety and health of employees.



Publication No. A-110C*

June 1981

GLACIAL ACETIC ACID CH₃COOH

CAS No. 64-19-7

Typical Properties^a

Molecular Weight (theoretical)	60.06
Wt/Vol, 20° C, lb/gal (U.S.) ^b	8.75
kg/L	1.05
lb/gal (Imperial)	10.5
Refractive Index, n _D ²⁵	1.3706
Viscosity, 25° C, cP	1.15
Vapor Pressure, 20° C, mm Hg	11.4
Boiling Point, 760 mm, °C (°F)	118.1 (244.6)
Coefficient of Expansion, 20° C	0.001070
Heat of Combustion, MJ/kg	14.6
Ionization Constant, 25° C	1.7 x 10 ⁻⁵
Solubility, 25° C, wt%	
in water	Complete
water in	Complete
Freezing Point, °C (°F)	16.6 (61.9)
Flash Point (Tag Open Cup), °C (°F)	43 (109)
(Tag Closed Cup), °C (°F)	39 (103)
Fire Point, °C (°F)	64 (148)
Autoignition Temperature, °C (°F)	516 (960)
Explosive Limits, mg/L	
Lower	142.6
Upper	378
(Acetic acid associates in the vapor phase)	
NFPA Code 30, Class	II
DOT Labels Required	Corrosive
DOT Classification	Corrosive material

*Replaces Eastman Publication No. A-110B.

^aReported for information only. Eastman makes no representation that the material in any particular shipment will conform exactly to the values listed.

^bWherever used elsewhere in this data sheet, "gallons" refers to U. S. measure.

Applications

Acetic acid is the most versatile of all organic acids. Among its important uses are the manufacture of cellulose acetate, vinyl acetate monomer, terephthalic acid, acetate-ester solvents, and pharmaceuticals. Other uses include pH adjustment in textile processing, pigment production and other industrial operations; photographic developing; and the production of metallic salts for use as catalysts and buffers.

Some major uses of acetic acid esters are as coatings, solvents, extraction solvents, and chemical intermediates. Since most of these have pleasant odors, many may be found in synthetic flavors and fragrances. Triacetin (glyceryl triacetate) is used in the preparation of pharmaceuticals, perfumes, and flavors, and as a plasticizer for cellulose and vinylidene polymers and copolymers.

Another major derivative is monochloroacetic acid (MCA), which is used in the manufacture of carboxymethyl cellulose (CMC) and pesticides such as 2,4-dichlorophenoxyacetic acid (2,4-D). MCA is also used in the synthesis of pharmaceuticals such as vitamin B-6.

Acetic acid is also used in the treatment of oil wells to improve the permeability of oil-bearing

formations. Other uses in the natural-resources industry include the production of flotation chemicals for phosphate rock, iron ore, and other minerals.

Reagent Grade Acetic Acid

Eastman produces a special grade of acetic acid to meet the specifications of the American Chemical Society's "Reagent Chemicals," Fifth Edition. Eastman Reagent Grade Acetic Acid is used in the semiconductor industry as a component of etching solutions, in chemical laboratories as a reagent, and in other industrial applications where an exceptionally pure grade of acetic acid is required.

Dilute Acetic Acid

Many acetic acid users prefer to store the material in diluted form to avoid the expense of heated storage tanks which are required for glacial acetic acid. Figure 3 demonstrates the rapid freezing-point depression achieved by the dilution of glacial acetic acid with water. Eastman Publication No. A-107 offers suggestions on the construction of storage vessels, unloading procedures, and dilution procedures for Eastman acetic acid.

Table 1
Dilution of Glacial Acetic Acid

To each 1000 pounds of glacial acetic acid (scale weight), add the quantities of water listed below.

Strength of Acetic Acid Required (% by wt)	Water To Be Added		Gallons of Dilute Acetic Acid Produced (at 68°F)
	Pounds	Gallons at 68°F (20°C)	
10	9000.0	1080.4	1184.8
20	4000.0	480.2	584.4
30	2333.3	280.1	385.1
40	1500.0	180.1	286.0
50	1000.0	120.0	226.9
56	785.7	94.3	201.5
60	666.7	80.0	187.9
70	428.6	51.5	160.4
80	250.0	30.0	140.1
82	219.5	26.3	136.7
84	190.5	22.9	133.6
90	111.1	13.3	125.0

Other strengths of dilute acetic acid can be obtained by using the following formula:

$$\text{Pounds water per 100 pounds glacial acetic acid} = \frac{(100 - \% \text{ acid required})}{\% \text{ acid required}} \times 100$$

Table 2
Dilution of Glacial Acetic Acid

For each 100 gallons of dilute acetic acid required,
blend the following quantities of glacial acid
and water:*

Strength Acetic Acid Required (% by wt)	Glacial Acetic Acid		Water	
	Scale Weight, Pounds	Measured Volume, Gallons	Scale Weight, Pounds	Measured Volume, Gallons
10	84.4	9.7	759.6	91.2
20	171.1	19.6	684.6	82.2
30	259.7	29.7	606.0	72.7
40	349.8	40.0	524.6	63.0
50	440.8	50.4	440.8	52.9
56	495.7	56.7	389.5	46.8
60	532.3	60.9	354.9	42.6
70	623.6	71.3	267.2	32.1
80	713.6	81.6	178.4	21.4
82	731.5	83.6	160.6	19.3
84	748.7	85.6	142.6	17.1
90	799.9	91.5	88.9	10.7

*If both ingredients are measured by volume, they must be measured at the **same temperature** to obtain the correct strength of dilute acetic acid.

If the quantity of **one** of the ingredients is determined by scale weight, the volume of the other should be measured at 68° F (20° C) to obtain the correct strength.

If both acid and water are weighed, the resultant volume of dilute acetic acid will be 100 gallons at 68° F.

(Compared to water at 39° F [4° C])

[illegible]

Figure 1
Specific Gravity of Acetic Acid at Various Concentrations

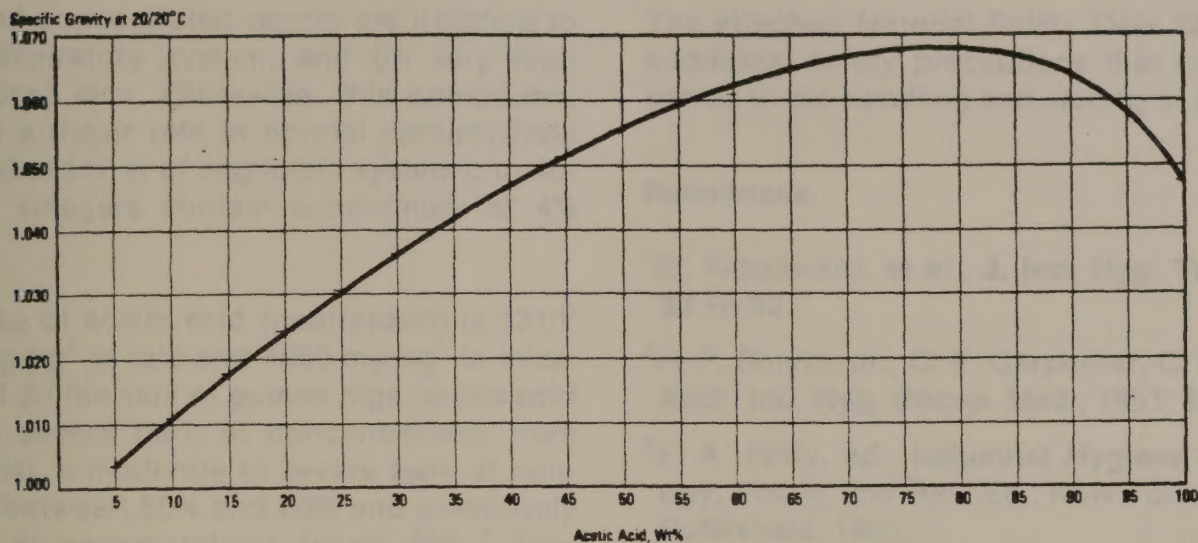


Figure 2
Weight of Acetic Acid Water Solutions, Measured at 20°C

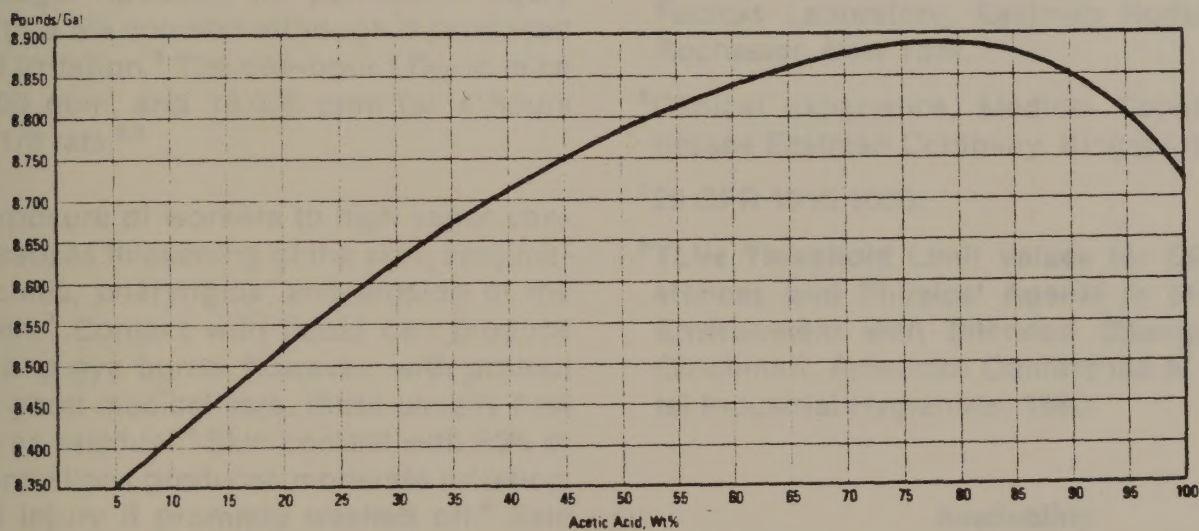
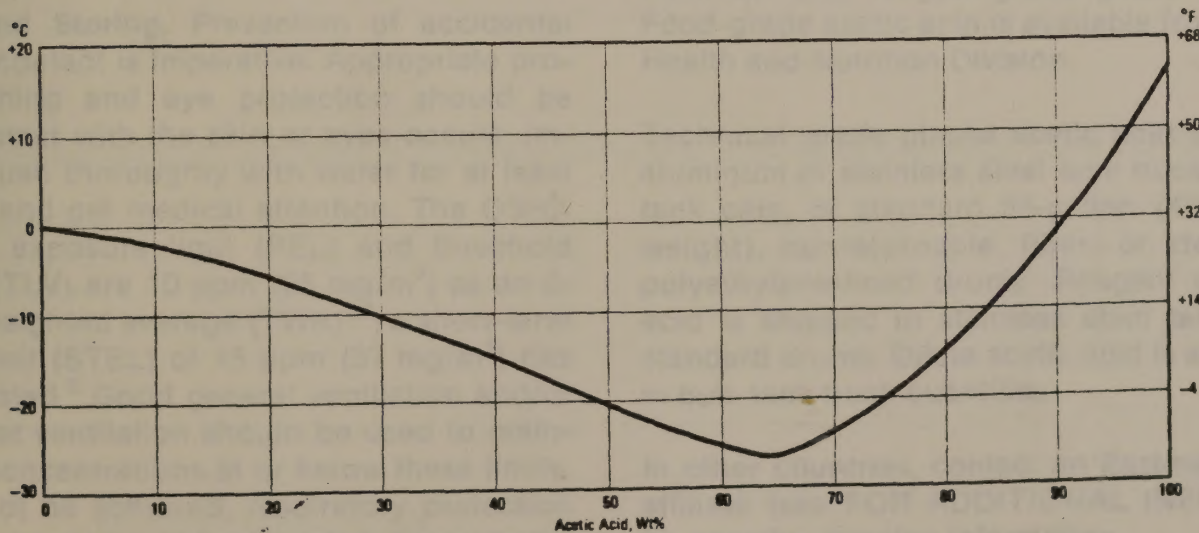


Figure 3
Freezing Point of Acetic Acid Water Solutions



Safety Precautions

Toxicity. Concentrated acetic acid solutions are corrosive and concentrated vapors are irritating to the eyes, respiratory system, and (in very high concentrations) skin. Otherwise, this compound, which plays a major role in normal carbohydrate and fat metabolism, is of negligible systemic toxicity. Natural vinegars contain a minimum of 4% acetic acid.

The oral LD₅₀ of acetic acid (neutralized) is 3310¹ and 3530 mg/kg² in rats and 4960 mg/kg¹ in mice. When tested on the skin of guinea pigs, acetic acid produced a severe burn at concentrations from 80% to glacial, a moderate to severe burn at concentrations between 50% and 80% and a relatively mild injury at concentrations below 50%.³ Ten-percent solutions are not significantly irritating to animal or human skin.⁴ When tested in the rabbit eye, concentrations as low as 10% produced permanent damage; however, no permanent injury was seen with a 5% solution although it produced severe initial irritation.⁵ The one-hour LD₅₀ in mice is about 5000 ppm, and 16,000 ppm for 4 hours was fatal to 1/6 rats.^{2,3}

Repeated exposure of workers to high vapor concentrations causes thickening of the skin, conjunctivitis, bronchitis, pharyngitis, and erosion of the exposed teeth.³ Contact with liquid can produce severe skin and eye burns; however, with prompt first aid and good medical care, these usually heal with little or no residual.⁶ Skin contact with 50% or lower concentrations produces moderate irritation, but minimal injury if promptly washed off.⁶ Skin sensitization has been reported but is extremely rare.³ Ingestion of concentrated solutions produces burns of the upper digestive tract.³

Handling and Storing. Prevention of accidental skin or eye contact is imperative. Appropriate protective clothing and eye protection should be worn. If contact with the skin or eyes occurs, immediately flush thoroughly with water for at least 15 minutes and get medical attention. The OSHA permissible exposure limit (PEL) and threshold limit value (TLV) are 10 ppm (25 mg/m³) as an 8-hour time-weighted average (TWA)^{7,8}; a short-term exposure limit (STEL) of 15 ppm (37 mg/m³) has been suggested.⁸ Good general ventilation and/or local exhaust ventilation should be used to maintain vapor concentrations at or below these limits. If this cannot be achieved, respiratory protection for organic vapor should be provided; since vapors

are irritating to the eyes, a full-facepiece respirator is recommended.

The attached Material Safety Data Sheet provides additional safety precautions that should be observed in the handling and storing of acetic acid.

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Availability

In the United States, the Industrial Chemicals Division of Eastman Chemical Products, Inc., markets technical and reagent-grade glacial acetic acid. Food-grade acetic acid is available from Eastman's Health and Nutrition Division.

Technical grade glacial acetic acid is shipped in aluminum or stainless steel tank trucks, aluminum tank cars, or standard 55-gallon (465-pound net weight), nonreturnable, fiber- or steel-jacketed, polyethylene-lined drums. Reagent grade acetic acid is shipped in stainless steel tank trucks or standard drums. Dilute acetic acid is available only in bulk tank truck quantities.

In other countries, contact an Eastman marketing affiliate (see FOR ADDITIONAL INFORMATION) for specific shipping information.

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1945

2. Beeswax cannot be kept in solution for intramuscular injection in a concentration greater than 4 per cent wax by weight in peanut oil. In this mixture, there is no tendency for the wax to separate from the oil.

3. No reaction occurred by scratch or intracutaneous tests with 4 per cent beeswax-peanut oil mixture in any of the patients who were tested, even though they had clinical hay fever or asthma due to one or more varieties of pollens. The prepared control solutions gave typical reactions.

4. Crude unfiltered beeswax and filtered beeswax gave no reactions in any of the patients who were clinically allergic and the results of the studies indicate that beeswax, combined with peanut oil because of its nonantigenic character, should be an ideal medium for delaying the absorption of penicillin when administered by subcutaneous or intramuscular methods.

I am indebted to E. B. Squibb and Sons who furnished the beeswax.

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ALLERGY TO CHEMICALS IN FLOUR

A CASE OF DERMATITIS DUE TO BENZOIC ACID

K. A. BAIRD, M.D., SAINT JOHN, N. B., CANADA

SKIN irritations peculiar to bakers have been known and described for over a century. Many cases of this bakers' dermatitis (bakers' itch, bakers' psoriasis) occurring among those exposed to wheat flour are known to be due not to wheat protein but to simple chemicals which are added for the purposes of bleaching the flour and preventing mold, or to other substances used in baking, such as spices, fruit juices, sugar, and flavoring agents.^{1, 2} Schweisheimer,³ described "bakers' dermatitis" as due to various agents, including so-called flour improvers. The chief improvers blamed were persulfates of ammonium and potassium. These, apparently are not used in Canada, but the article mentions that an outbreak of dermatitis occurred among bakers in New South Wales within a few months after the introduction of these substances to the activators used in doughmaking. It continued while the persulfate was used.

The following case is that of a baker whose allergic contact dermatitis was elicited by external exposure to flour. In this case the eruption was not caused by wheat proteins but by infinitesimal traces of an incorporated simple chemical, namely, benzoyl peroxide, or rather its residue, benzoic acid.

It has proved possible for the patient to continue his occupation as long as he uses a flour which contains no benzoic acid residue.

CASE REPORT

H. M., a young adult who had spent a good many years as a baker and recently had operated his own home bakeshop, developed periods of asthmatic wheezing and an increasingly severe skin rash for about one year. He was given some intradermal skin tests and told that he was sensitive to wheat. He was also given some inoculations in an attempt to hyposensitize him, with possibly some relief of his asthmatic symptoms. The rash, however, became worse.

When first seen by the author on July 14, 1943, he had been in the hospital for two weeks. He thought the rash had become worse in spite of treatment. He had a very severe dermatitis on his arms, shoulders, face, neck, and on the front of his chest. This extended over the areas which would be exposed while he worked in the shop wearing only a light, open-necked shirt. He had not been troubled with asthma for several weeks. Acting on the impression (which could not be proved) that the rash was being maintained, in part, by a low grade staphylococcal infection, the patient was given a course of mixed sensitized vaccine in addition to protection of the severely irritated areas by soothing ointment under a dressing. Wheat was removed from his diet. Rapid improvement permitted him to return home in about ten days. He continued to improve until the skin became practically clear. He reopened his bakery and tried to avoid direct contact with flour, but, at various times during August and September when he was exposed to the flour dust, the dermatitis recurred. He thought the bread flour irritated more than cake and pastry flour, the gluten content of which is higher. He also noticed a little asthmatic wheezing after these exposures. The possibility that his sensitivity was due not to the wheat protein but to the improvers in the flour deserved some attention. He brought samples of cake, bread, and pastry flours of the type ordinarily used in the business and which were said to contain "improvers." He also brought a sample of a flour which did not contain "improvers." Patch tests were done with these four varieties of flour by wetting a small quantity and holding it on the skin of the front of the chest with a pledget of absorbent cotton and a square of adhesive plaster. At the end of twenty-four hours the three improved flours had each produced an area of tiny papules which was slightly itchy and very much resembled the areas of skin where the rash began to develop when the patient was exposed to flour dust in his bakeshop. The "non-improved" flour did not produce any apparent reaction. The patient was advised to clear all traces of the "improved" flours out of his shop and lay in a stock of "nonimproved" flour.

At about this time a kind friend advised him so strongly to go elsewhere for treatment that he went to one of the larger cities on the continent where he was seen by a very good dermatologist who referred him for examination to an otolaryngologist and an allergist. The former felt he had chronic septic tonsillitis.

The allergist did tests for approximately sixty articles of food and contactants which seemed possible allergens. Many were done by both scratch and intradermal methods. The positive reactions (to intradermal) of any consequence were as follows:

Barley, 7 plus	Corn, 3 plus	Oats, 3½ plus
Wheat, 10 plus	Yeast, 8 plus	String beans, 4 plus
Chicken, 6 plus	Stock dust, 10 plus	Virginia tobacco, 4 plus
Short ragweed, 2 plus		Mixed grass, 6 plus

He suggested various measures for the avoidance of these substances and suggested that the patient might be helped by a course of histamine-azo-protein.

In the meantime the author had written the Department of Agriculture in Ottawa and received the following information:

Most millers now bleach flour and add about five parts per million of potassium bromate. Bleaching is done by one or more of three agents:

Nitrogen trichloride in proportion of about one or two grammes per barrel reacts with the flour to produce hydrochloric acid and ammonia. Nitrogen peroxide is usually produced by an electric spark

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giving nitrite as an end product, but in so trifling an amount that it is difficult to be sure whether the nitrite found in the flour is a natural constituent or the result of the reaction. When benzoyl peroxide is used the residue from this material acting on the flour is benzoic acid, the quantity being about ten parts per million.

After returning home the patient decided to take the author's advice and change to nonimproved flours. Since doing this he has been getting along very well. He eats wheat bread. On some occasions he develops a slight papular rash on his arms or chest, but apart from making him slightly apprehensive lest the old severe dermatitis should return this does not affect him seriously. He is unable to correlate the appearance of this rash with any exceptional exposures to anything. He feels rather sure that handling or eating commercial jams and pickles is followed by some skin reaction. These often contain sodium benzoate as a preservative!

Patch tests done with potassium bromate and benzoic acid in water gave no significant reaction. A patch test of 6 per cent benzoic acid in liquid petrolatum was applied. A very definite papular rash appeared in about six hours. This increased and became rather annoying so that, at about the end of sixteen hours, the patient removed the patch. Some ten hours after that, the area of the patch could be clearly seen as a slightly inflamed rectangle with a goodly number of papules. A control test with liquid petrolatum alone was negative.

After considerable correspondence the following information was obtained from the Department of Agriculture and Department of Health and Welfare, at Ottawa.

Government regulations require that the residual benzoic acid in flour shall not exceed seventy-five (75) parts per million calculated as benzoic acid (C_6H_5COOH).

Of seven samples of bleached flour from six companies examined by the Division of Chemistry (Department of Agriculture) several years ago, five contained benzoyl peroxide. The amounts varied from traces to 45 p.p.m. expressed as benzoic acid.

When Novadelox (the bleaching agent containing benzoyl peroxide) was not used, no benzoic acid was found in the flour.

The Assistant Director of Research for the makers of Novadelox indicated he had never heard of a case where benzoic acid was said to cause bakers' dermatitis. He estimated that $\frac{3}{8}$ of an ounce of their product per barrel of flour would yield not more than 18 parts per million. This information was obtained through courtesy of the company whose three flours gave positive patch tests and seemed to be the cause of the trouble in the case under discussion. Correlating it with the results of the Department of Agriculture's figures we must conclude that, in some cases, as much as $1\frac{1}{12}$ ounce per barrel must be used by some flour companies to give the 45 parts per million previously reported.

The makers of the flour which gave no positive skin test, and which the patient has been using for over a year without getting dermatitis, object greatly to the use of so-called improvers such as potassium bromate. Therefore, they do not use them but state that they subject their commercial flour to a *very light* treatment of "Novadel." They also indicate that the possible *trace* of benzoic acid which results would be further reduced because their flour remains in storage for a period before shipment.

It seems fair to conclude that what at first seemed an allergy to wheat, and later to potassium bromate, was really due to benzoic acid from the bleaching agent. The benzoic acid was present in such slight trace (if at all) in the second flour used that it was innocuous. The commercial jams and pickles, which the patient suspected, usually contain benzoate of soda.

During the month of February, 1945, this baker was unable to obtain the "unimproved" flour which he had been successfully using for over a year, so he bought a bag of the usual standard commercial "improved" flour. He very promptly developed several areas of dermatitis on both hands and a slight amount of papular rash across the base of his neck and on the front of his chest. The rash disappeared rapidly after he reverted to the nonimproved flour. This event seems to be an additional control test, corroborating the fact that he is sensitive to the one flour and not to the other.

SUMMARY

1. A baker, who developed dermatitis from "improved" flours which also contained traces of benzoic acid, and who showed positive intradermal skin tests to wheat, was able to work with "nonimproved" flour containing little if any benzoic acid.
2. Patch tests corroborated this difference in sensitivity to the two types of flour.
3. Patch tests did not show hypersensitivity to potassium bromate but did show contact type eczematous hypersensitivity to benzoic acid.
4. The conclusion that this is a case of allergic contact type dermatitis due to benzoic acid seems justified.

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Place the prepared chalk in a mortar and triturate until free from lumps. Add bentonite magma in small portions, triturating thoroughly after each addition until a uniform mixture results. Then add the peppermint water in which the soluble saccharin has been dissolved; transfer this to a graduated vessel and rinse the mortar with enough distilled water to make the product measure 100 cc. Mix thoroughly.

This product is entirely palatable and yields satisfactory preparations when combined in prescription form with elixir of phenobarbital, elixir of Nembutal, compound elixir of pepsin, elixir of pepsin and rennin, Liquid Takadiastase, Caripeptic Liquid, camphorated tincture of opium, milk of magnesia, milk of bismuth, aluminum hydroxide gel, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, Kaomagma, Kaopectate and tincture of belladonna. Addition of tincture of opium causes excessive thickening.

SUMMARY AND CONCLUSIONS

1. Chalk mixtures containing prepared chalk, soluble saccharin, cinnamon water,

distilled water and variable amounts of bentonite were prepared. The bentonite seems superior to the more expensive acacia as a suspending agent for this purpose; concentrations between 0.9% and 2.4% are most suitable. Elimination of fermentable materials (sucrose and acacia) produced a biologically stable preparation, but some samples after long standing developed odors resembling toluene.

2. The toluene-like odor is not produced when cinnamon water is replaced by peppermint water.

3. An improved formula for chalk mixture containing prepared chalk, bentonite (magma), soluble saccharin, peppermint water and distilled water is suggested. This product is palatable and is compatible with many of the drug preparations that are prescribed with chalk mixture.

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The Toxicity of Benzoic Acid for White Rats*

By George P. Hager,[†] C. W. Chapman and E. B. Starkey

Benzoic acid is widely used in the preservation of food products (1) and pharmaceutical preparations (2), especially those with an acid reaction. Furthermore, because of its antiseptic action, it is used in ointments and dusting powders for the treatment of skin infections, in a 1% solution as a mouth wash (3), in a 0.5% solution for the treatment of chronic suppurating wounds (4) and in preparations for the treatment of tuberculosis, asthma and rheumatism (1).

In view of these many varied uses of benzoic acid, much interest attaches to its toxicity. It has been found that a rather broad

margin of safety attends its use in these instances—0.5 Gm. daily produced no demonstrable effects in healthy persons and even 4 Gm. was not injurious (5, 6). Amounts far in excess of the quantities likely to be consumed with food are required to produce ill effects or cause the death of human beings or experimental animals. However, benzoic acid, one of the least harmful of food preservatives, should be avoided by persons with gastro-intestinal or renal diseases (7). Many attempts have been made to prepare compounds related to benzoic acid with even greater margins of safety in the preservation of food. For the purpose of comparing the effect of benzoic acid with that of certain of its substitution derivatives, a preliminary study of the acute toxicity of these compounds for white rats was undertaken.

* From the School of Pharmacy, University of Maryland, Baltimore, Md.

Presented to the Scientific Section of the A. Ph. A., Detroit meeting, 1941.

[†] Wm. R. Warner Fellow, 1939-41, University of Maryland.

EXPERIMENTAL

A portion of the results of this work is the subject of this report. For the comparison of the value of the LD_{50} for white rats found in this investigation with the statements on the toxicity of this substance for human beings and various experimental animals reported in the literature, Table I was drawn up. These other results do not include a measure of the standard deviation and, therefore, the significance of the differences of the reported values cannot be calculated.

Table I.—Summary of the Investigations of the Acute Toxicity of Benzoic Acid

Subject	Dose	Effect
Dogs, cats, rabbits ^a	2 Gm./Kg.	Lethal dose
Rabbits (dry-fed) ^a	1.7 Gm./Kg.	Lethal dose
Rabbits (fasting) ^a	1.52 to 1.83 Gm./Kg.	Lethal dose
Guinea pigs (intra-peritoneal) ^a	1.4 Gm./Kg.	Lethal dose
White rats (intra-venous)	1.714 $\pm$ 0.037 Gm./Kg.	LD_{50}
Human ^b	1 to 1.5 Gm. (capsule)	Gastric pain, nausea and vomiting

^a See reference (8).

^b See reference (9).

The method of determining the acute LD_{50} reported here for white rats consisted in injection of an aqueous solution of sodium benzoate of appropriate concentration into the saphenous vein at a rate of 1 cc. per min. Five doses were employed in each test, the first of which was likely to kill none of the animals injected and the last of which was likely to kill all of the animals injected. The doses differed by a constant ratio, the logarithm of which was 0.07; and varied from 1.2 to 2.29 Gm./Kg. Each dose was administered to a group of five rats weighing from 90 to 150 Gm. The solutions employed were of such concentration (12% to 23%) that the dose, based on the weight of the rat, would be contained in about 1 cc. The solutions were prepared by dissolving the highly purified acid in a solution of an equivalent weight of sodium carbonate. Results were recorded hourly for 5 to 6 hrs. to ascertain rate of onset of action, symptoms, etc., and the LD_{50} calculated from the number of animals dead in 24 hrs.

The symptoms of benzoic acid poisoning observed during the course of these experiments were those resulting from a heightening of the reflexes of the central nervous system, and consisted of tremors, clonic and often tetanic convulsions, with death occurring during a remission. These symptoms appeared within a few minutes after the injection and progressed rapidly with deaths often occurring one-half to one hour after injection. Surviving animals generally showed none of the nervous manifestations, but salivation, vomiting and diarrhea were present. A marked diuresis was seen in some cases.

For the calculation of the LD_{50} from these experiments, the use of the maximum likelihood method for the statistical treatment of biological results would be very cumbersome and would likely give values much different from those obtained by the less exacting method. Therefore, the LD_{50} 's were calculated by Kärber's method (10); and the standard deviation of the individual determinations was obtained after first fitting the observed mortalities to a straight line by a method developed by Irwin and Cheeseman (11). The weighted mean of the values thus obtained in three separate determinations was calculated. The standard error of the mean was then obtained in the usual manner. In a different set of experiments carried out in the same way and on the same days, the toxicity of a fluorine substituted benzoic acid was studied. The results of these experiments are summarized in Table II.

TABLE II

Benzoic Acid	p-Fluorobenzoic Acid
$LD_{50} \pm S. D., \text{ Gm./Kg. } (P = 0.66)$	
1.686 $\pm$ 0.105	1.982 $\pm$ 0.137
1.855 $\pm$ 0.076	1.687 $\pm$ 0.109
1.630 $\pm$ 0.062	1.434 $\pm$ 0.055
$\text{Weighted Mean } (LD_{50} \pm S. E.), \text{ Gm./Kg.}$	
1.714 $\pm$ 0.062	1.542 $\pm$ 0.107
($P = 0.66$)	($P = 0.66$)
1.714 $\pm$ 0.124	1.542 $\pm$ 0.214
($P = 0.95$)	($P = 0.95$)

In experiments of this type in which a small number of animals and a large number of doses are employed, it has been shown that the values obtained by the maximum likelihood method of calculation and by the method outlined above are very close (11).

By plotting the percentage mortalities observed in an individual determination, as ordinates, against the corresponding doses expressed as a logarithm of the ratio of the doses to the LD_{50} calculated from the experiment, the results of the three experiments can be combined in a single curve, the regression line. This can be conveniently done by plotting the percentage mortalities against the ratio on logarithmic probability paper (Fig. 1). Seventy-five animals were employed in the construction of this curve, and its steepness indicates a great uniformity in the response of white rats to benzoic acid.

The significance of the differences between the individual determinations and between the mean values was calculated by the formula

$$\frac{m_1 - m_2}{\sqrt{(S. E._1)^2 + (S. E._2)^2}}$$

where m is an individual LD_{50} or a weighted mean LD_{50} and $S. E.$ is the standard deviation of the corresponding individual LD_{50} or the standard error of the corresponding weighted mean LD_{50} . When the value of this quotient is 2 or greater, the difference between m_1 and m_2 is generally considered significant. That is to say that when the value is 2 or greater, the

Figure 1.—Regression of Benzoic Acid

- (1) Kaufmann, 1919), 199.
- (2) Labat, A., 1922), 104; through
- (3) Bleacher, C., 1928.
- (4) Taylor, K.
- (5) Chittenden, C. A., U. S. Dept. of Health, 1913.
- (6) Herter, C., 1910), 1774.

ALFRED J. ASGIS, *et al.*
Society. Clin. Soc. New York, 1941. 29
MILES ATKINSON, Charles Scribner's Sons, + 348 pp. \$3.00
DAVID L. BELDING, D. Appleton-Century Co., 1942. xxi + 88
HUGH R. BUTT, W. B. Saunders Co., 1941. x + 172 pp.

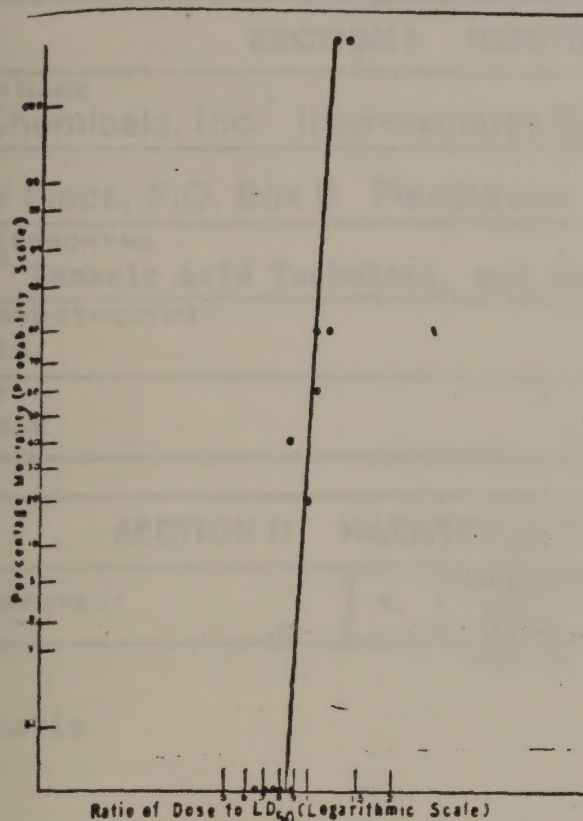


Figure 1.—Regression Line for the Action of Benzoic Acid on White Rats.

observed difference could occur through chance or through an error in sampling only once in twenty times; and the chances are twenty to one that a greater toxicity is to be assigned to the substance whose LD_{50} is m_1 than to that whose LD_{50} is m_2 . The application of this formula showed that no significant difference exists between the three values of the LD_{50} determined for benzoic acid. Likewise was the difference between the LD_{50} found for benzoic acid and that found for *p*-fluorobenzoic acid shown to be insignificant. On this basis, one is justified only in saying that benzoic acid and *p*-fluorobenzoic acid were found in these experiments to be of the same toxicity even though the absolute value of the weighted mean LD_{50} of benzoic acid is greater than that of *p*-fluorobenzoic acid. The use of statistical methods is therefore seen to be of great value in the study of the relation of chemical structure and physiological activity from a quantitative standpoint.

SUMMARY

The toxicity of benzoic acid when administered as the sodium salt intravenously to white rats corresponds closely to that reported for other animals. The value of the LD_{50} found in this investigation is 1.714 ± 0.124 Gm./Kg. ($P = 0.95$).

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- (1) Kaufmann, H. P., *Z. angew. Chem.*, 32 (1919), 199.
- (2) Labat, A., *Bull. soc. pharm. Bordeaux*, 60 (1922), 104; through *Chem. Abstracts*, 16, p. 4006.
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- (4) Taylor, K., *Lancet*, I (1917), p. 294.
- (5) Chittenden, R. H., Long, J. H., and Herter, C. A., U. S. Dept. Agr. Rept. No. 88 (1909), p. 13.
- (6) Herter, C. A., *J. Am. Med. Assoc.*, 54 (1910), 1774.
- (7) Sollmann, T., "A Manual of Pharmacology," W. B. Saunders Company, Philadelphia, Pa. 1936, pp. 601-603.
- (8) Heffter, A., "Handbuch der experimentellen Pharmakologie," Julius Springer, Berlin, 1923, p. 972.
- (9) Wiley, H. W., U. S. Dept. Agr. Bur. Chem. Bull. No. 88, (1908), p. 1043.
- (10) Kärber, G., *Arch. expil. Path. Pharmacol.*, 162 (1931), 480.
- (11) Irwin, J. O., and Cheeseman, E. A., *J. Hyg.*, 39 (1939), 574.

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To July 15, 1942

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| ALFRED J. ASGIS, <i>Professional Dentistry in American Society</i> . Clinical Press, 1123 Broadway, New York, 1941. 260 pp. \$4.50. | ERNEST CHILD, <i>The Tools of the Chemist</i> . Reinhold Publishing Corporation, 330 West Forty-second Street, New York, 1940. 220 pp. \$3.50. |
| MILES ATKINSON, <i>Behind the Mask of Medicine</i> . Charles Scribner's Sons, New York, 1941. xiv + 348 pp. \$3.00. | FORREST RAMON DAVISON, <i>Synopsis of Materia Medica, Toxicology and Pharmacology for Students and Practitioners of Medicine</i> . Second edition. The C. V. Mosby Company, St. Louis, 1942. 695 pp. \$5.75. |
| DAVID L. BELDING, <i>Textbook of Clinical Parasitology</i> . D. Appleton-Century Company, Inc., New York, 1942. xxi + 888 pp. \$8.50. | <i>Drug and Cosmetic Review, 1942-1943</i> . Sixth edition. Drug and Cosmetic Industry, 101 West Thirty-first Street, New York, 1942. \$3.00. |
| HUGH R. BUTT and ALBERT M. SNELL, <i>Vitamin K</i> . W. B. Saunders Company, Philadelphia, 1941. i + 172 pp. | CARY EGGLESTON, <i>Essentials of Prescription Writing</i> . |



MATERIAL SAFETY DATA SHEET

77

(Approved by U.S. Department of Labor as "essentially similar" to FORM OSHA-20)

SECTION I IDENTIFICATION OF PRODUCT

MANUFACTURER'S NAME Tenneco Chemicals, Inc. Intermediates Division		EMERGENCY TELEPHONE NO. (201) 779-0570
ADDRESS Turner Place, P.O. Box 2 Piscataway, New Jersey 08854		
TRADE NAME AND SYNONYMS Benzotek (R) Benzoic Acid Technical, and Benzoic Acid U.S.P.		
CHEMICAL NAME AND SYNONYMS Benzoic Acid		
CHEMICAL FAMILY Aromatic Acid	MOLECULAR FORMULA C₆H₅COOH	MOL. WT. 122.12

SECTION II HAZARDOUS COMPONENTS OF MIXTURES

COMPONENT	%	THRESHOLD LIMIT VALUE	COMPONENT	%	THRESHOLD LIMIT VALUE
		(UNITS)			(UNITS)
Not applicable					

SECTION III PHYSICAL DATA

APPEARANCE AND ODOR Nearly white flakes, slight aromatic odor (U.S.P.) White crystals or fine powder, almost odorless..	
BOILING POINT (DEGREES FAHRENHEIT) 480°F	MELTING POINT (DEGREES FAHRENHEIT) 251°F
VAPOR PRESSURE (MM. OF MERCURY) 1 mm. at 205°F 5 mm. at 247°F	SPECIFIC GRAVITY (WATER = 1) 1.316 at 82°/39°F. 1.052 at 311°/39°F.
VAPOR DENSITY (AIR = 1) 4.2	PERCENT VOLATILE (BY WEIGHT) Essentially not volatile
SOLUBILITY IN WATER Negligible (0.34% at 77°F)	EVAPORATION RATE (BUTYL ACETATE = 1) Not applicable

SECTION IV FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (SPECIFY METHOD) (DEGREES FAHRENHEIT) 250°F. closed cup	FLAMMABLE LIMITS (PERCENT BY VOLUME) Not available	LOWER	UPPER
FIRE EXTINGUISHING MEDIA Water spray, carbon dioxide or dry chemical.			
SPECIAL FIRE-FIGHTING PROCEDURES Water spray or fog for large fires or benzoic acid dust.			
UNUSUAL FIRE AND EXPLOSION HAZARDS Vapor from molten benzoic acid may form explosive mixture with air. Concentrated dust may form explosive mixture.			

This information is furnished without warranty, representation, inducement or license of any kind, except that it is accurate to the best of Tenneco Chemicals' knowledge or obtained from sources believed by Tenneco Chemicals to be accurate, and Tenneco Chemicals does not assume any legal responsibility for use or reliance upon same. Customers are encouraged to conduct their own tests. Before using any product read its label.

SECTION V HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE

None established.

EFFECTS OF OVEREXPOSURE

Dust and vapor cause irritation of eyes nose and throat. Prolonged contact with skin may cause irritation and have a keratolytic effect. Acute and chronic toxicity by ingestion is low, aside from local irritation.

AGENCY AND FIRST AID PROCEDURES

If inhaled, remove to fresh air. In case of contact, flush with plenty of water, wash skin with soap and water. If swallowed, induce vomiting with warm salt water.

SECTION VI REACTIVITY DATA

STABILITY	UNSTABLE		CONDITIONS TO AVOID High concentrations of dust or vapor from molten material form explosive mixtures with air. Avoid exposure to sparks and open flame.
	STABLE	X	
COMPATIBILITY (Materials to avoid) Reacts with alkalies. Keep dry. Moisture may cause caking.			
HAZARDOUS DECOMPOSITION PRODUCTS Burning may produce irritating vapors and carbon monoxide.			
HAZARDOUS POLYMERIZATION	MAY OCCUR		CONDITIONS TO AVOID Discolors slowly in molten state and decomposes slowly above 300°F.
	WILL NOT OCCUR	X	

SECTION VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED

Provide ventilation and use dust respirator in dusty conditions. Sweep up and remove to disposal container. Flush area with water. If molten, allow to solidify before removing. Keep flames away.

WASTE DISPOSAL METHOD

Incinerate in a suitable furnace or bury with lime in an approved landfill. Observe local, state and federal regulations, and do not contaminate any streams, lakes or ponds.

SECTION VIII SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (Specify type)

In high concentrations, use dust respirator, or Bureau of Mines approved respirator for acid vapors in case of vapor.

VENTILATION	LOCAL EXHAUST Required for dusty operations	SPECIAL Scrubber for dust on vapor exhaust
	MECHANICAL (General) Acceptable for small volume	OTHER None
PROTECTIVE GLOVES Gloves to minimize skin contact.		EYE PROTECTION Safety goggles. Face shield for molten.
OTHER PROTECTIVE EQUIPMENT Wash fountain. Wash contaminated clothing before re-use.		

SECTION IX SPECIAL PRECAUTIONS

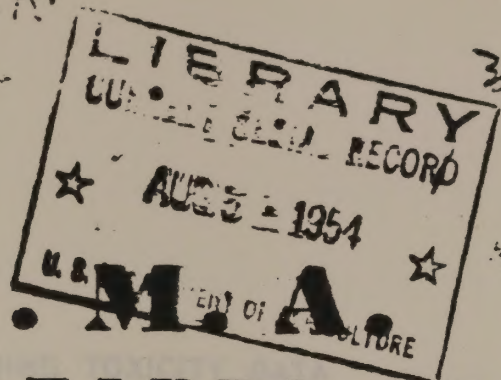
PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING

CAUTION!

Avoid Contact with eyes and skin.
Avoid breathing dust.
May cause irritation.

49.8
v24
etc

A.M.A.



A.M.A. **ARCHIVES OF** **Industrial Hygiene** **and** **Occupational Medicine**

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JULY 1954
VOLUME 10 NUMBER 1

IN TWO SECTIONS—SECTION I

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RANGE-FINDING TOXICITY DATA

List V

HENRY F. SMYTH JR., Ph.D.

CHARLES P. CARPENTER, Ph.D.

CARROL S. WEIL, M.A.

AND

URBANO C. POZZANI, M.S.

PITTSBURGH

SINCE the appearance of our previous communications on the range-finding test,* additional data from our work have become available for presentation. They are listed in the Table. All materials named either are being handled in commercial quantities or have been tentatively evaluated for specific commercial applications within the past few years. A few are known by trade names not suggested by the chemical names given here. In particular, Cellosolve compounds are tabulated as oxyethanols; Carbitol compounds appear as oxyethoxyethanols, ethanolamines as substituted 2-aminoethanols, and diethanolamines as substituted 2,2'-iminodiethanols.

It should be emphasized that the range-finding test is relied upon only to allow predictions of the comparative hazards of handling new chemicals. Acute toxicity studies, no matter how carefully planned, yield no more than indications of the degree of care necessary to protect exposed workmen and indications that certain technically feasible applications of a chemical may or may not eventually be proved safe.

It appears inevitable that minor changes in details will take place in any method which is employed for a period of years. For that reason, as well as to save reference to the earlier papers in this series,† the methods used for obtaining the data of the Table are briefly described again.

Single dose oral toxicity for rats is estimated by intubation of dosages in a logarithmic series to groups of five male rats or at times to female rats. The animals are Carworth-Wistar rats, raised in our own colony, fed Rockland rat diet complete, weighing 90 to 120 gm., and not fasted before dosing. Chemicals are diluted with water, corn oil, or a 1% solution of sodium 3, 9-diethyl-6-tridecanol sulfate (Tergitol Penetrant 7) when necessary to bring the volume given one rat to between 1 and 10 ml. Fourteen days after dosing, mortality is considered complete. The most

From the Mellon Institute of Industrial Research, University of Pittsburgh.

*References 1 to 4.

†References 1 to 4.

Vinyl 2-ethylhexyl ether.....	1.35 (1.17-1.50)	3.50 (2.20-5.70)	1 hr.		..	...	3	1
Vinyl 2,6,8-trimethylnonyl ether.....	1.22 (0.98-1.52)	5.0	1 hr.		..	...	5	1
Vinyl 2-methoxyethyl ether.....	3.90 (3.49-4.30)	7.13 (4.41-11.52)	1 hr.	8,000	4	4/6	1	2
2-Ethoxy-4-methyl-2,3-dihydro-4H-pyran.....	3.40 (3.11-3.72)	1.00 (0.63-1.79)	4 hr.		..	...	3	2
1,2-Dibutoxyethane.....	3.25 (2.82-3.74)	3.50 (2.20-5.70)	8 hr.		..	...	4	2
2,2'-Dibutoxyethyl ether.....	3.90 (3.35-4.50)	4.04 (3.41-7.40)	8 hr.		..	...	3	2
1-Butoxy-2-ethoxyethane.....	2.83 (1.93-4.15)	2.12 (1.20-3.50)	2 hr.		..	...	2	4
2-Butoxyethyl vinyl ether.....	3.10 (2.77-3.40)	3.00 (2.13-4.21)	4 hr.	2,000	8	2/6	2	5
1,1-Dibutoxyethane.....	8.79 (7.00-9.70) †		8 hr.		..	...	5	1
1,1-Di(2-methoxyethoxy)ethane.....	3.20 (2.73-3.90)	4.24 (2.52-7.12)	8 hr.		..	...	1	1
1,1,3-Trimethoxybutane.....	1.48 (1.35-1.62)		2 hr.	2,000	4	1/6	2	2
Epoxy Compounds								
1,2,3,4-Diepoxybutane.....	0.078 (0.059-0.102)	0.080 (0.055-0.144)	15 min.		..	...	6	0
Diisobutylene oxide.....	4.02 (3.75-4.40)	14.1 (8.7-22.9)	10 min.	4,000	4	2/6	1	2
Phenyl glycidyl ether.....	4.20 (3.90-4.60)	1.50 (1.07-2.10)	8 hr.		..	...	5	2
Epoxyethylbenzene.....	4.29 (3.07-5.98)	1.06 (0.63-1.79)	1 hr.	500	4	2/6	2	2
Ketones								
Pentanone-3.....	2.14 (1.54-2.90)	20	15 min.	8,000	4	4/6	2	4
Hexanone-2.....	2.59 (2.11-3.18)	5.99 (4.27-8.42)	30 min.	4,000	4	0/6	1	3
5-Ethyl-3-nonen-2-one.....	8.12 (7.27-9.00)	8.48 (5.04-14.24)	8 hr.		..	...	2	1
Aldehydes								
Isobutyraldehyde.....	3.73 (2.68-5.21) †	7.13	15 min.	8,000	4	1/6	1	5
Hexanal.....	4.80 (4.52-5.04)		1 hr.	2,000	4	1/6	2	2
Hexa-2,4-dienal.....	0.73 (0.61-0.86)	0.27 (0.16-0.45)	15 min.	2,000	4	1/6	6	8
2-Methyl-2-pentene-1-al.....	4.29 (3.07-5.99)	4.5 (2.0-9.8)	1 hr.	2,000	4	3/6	2	5
3-Methylglutaraldehyde.....	0.78 (0.40-1.31)	0.30 (0.14-0.67)	8 hr.		..	...	6	9
α -Hydroxyadipaldehyde.....	17.0 (12.2-23.8)	> 20	8 hr.		..	...	2	1
3,3,5-Trimethylcyclohexanecarboxaldehyde.....	4.14 (3.18-5.38)	15.8	8 hr.		..	...	4	2
Acids, Anhydrides, Lactones								
Propionic anhydride.....	2.86 (2.06-2.71) †	10.0 (5.8-19.0)	1 hr.		..	...	2	6
Butyric acid.....	8.79 (8.06-9.58) †	6.35 (3.94-10.28)			..	...	5	0
3-Methoxybutyric acid.....	3.03 (2.44-3.75)		8 hr.		..	...	4	8
2-Ethylbutyric acid.....	2.20 (1.07-2.40) †	0.52 (0.38-0.75)	8 hr.		..	...	2	9
Hexanoic acid.....	0.44 (5.77-7.19)	0.63 (0.33-1.20)	8 hr.		..	...	6	8
2-Methylpentanoic acid.....	2.04 (1.82-2.27)		8 hr.		..	...	4	9
3-Butoxypropionic acid.....	5.19 (4.20-6.41)	0.63 (0.43-0.94)	8 hr.		..	...	4	9
Hexanoic acid, ϵ -lactone.....	4.29 (3.07-5.98)	5.99 (4.27-8.42)	8 hr.		..	...	1	8
3(2-ethylbutoxy)propionic acid.....	3.73 (2.43-5.74)	0.53 (0.38-0.75)	4 hr.		..	...	6	8
3,5-Dimethyl-3-hydroxy-4-hexanoic acid, β -lactone.....	2.70 (2.34-3.11)		4 hr.		..	...	1	5
3(2-ethylhexyloxy)propionic acid.....	3.73 (2.68-5.21)	0.75 (0.54-1.06)	8 hr.		..	...	6	7
3-Cyclohexene-1-carboxylic acid.....	4.26 (3.65-4.98)	1.00 (0.68-1.48)	4 hr.		..	...	6	9

TOXICITY OF SOME ALIPHATIC ACIDS AND ESTERS

the application to the intact human skin is followed only after 52 minutes by very moderate burning, and erythema and hyperemia are hardly noticeable; this is followed within 24 hours by slight scaling of the epidermis.

Absorption, Fate and Excretion.—Butyric acid is absorbed from the gastrointestinal tract, but other routes of absorption have apparently not been studied. As to its fate in the metabolism, Marx (1910) found that its oral administration to fasted dogs results occasionally and its intraperitoneal injection regularly in the excretion of acetoacetic acid, and that this ketogenic action is less marked in animals fed carbohydrates. Blum (1910) showed that in dogs the subcutaneous injection of butyric acid results in the excretion of β -hydroxybutyric acid, acetoacetic acid, and acetone; the β -hydroxybutyric acid being presumably formed secondarily from acetoacetic acid. Ehrmann (1913) found acetoacetic acid and acetone in the urine of rabbits after oral administration of butyric acid. Bloch and Ritterberg (1944) showed that, after oral administration to rats, a considerable portion of butyric acid is metabolized to acetic acid. Experiments of Rittenberg, Schoenheimer and Evans (1937) indicate that this oxidation takes place rapidly. It evidently takes place in the liver, as indicated by perfusion experiments with this organ by Embden, Salomon, and Schmidt (1906), and Embden and Engel (1908), and the experiments with liver slices and liver juice as reported by Leloir and Munoz (1939). From the reports of Ciaranfi (1938) and Kleinzeller (1943) it appears, however, that similar oxidative processes may also take place in the kidneys. Experiments reported by Buchanan, Hastings and Nesbett (1943) with rats show that oral administration of butyric acid will increase the glycogen content of the liver.

Toxicity of Butyric Acid for Animals.—Butyric acid causes a depression of the central nervous system, as demonstrated in frogs by Fodera (1894) and Sternberg

(1898). According to the latter, doses of 0.1 gm. cause only clumsy movements, doses of 0.3 gm. prolonged depression, and doses of 0.5 gm. profound depression, followed by death after several days. Similarly Mayer (1886) reported that in rabbits the intravenous administration of 1.6 gm/kg. of sodium butyrate causes a marked temporary depression of the central nervous system. According to the same author the intravenous injection of 0.86 gm/kg. of sodium butyrate, given as 30% solution, causes in dogs vomiting, staggering, and deep sleep lasting one hour. Similar effects were produced in cats after subcutaneous doses of 0.5 gm/kg. (given as 10% solution). Marx (1910) and Ehrmann (1911, 1913) pointed to the similarity between diabetic coma and the toxicological picture produced by the intravenous injection of butyric acid.

Ehrmann and Esser (1911) found that the oral administration of small doses of sodium butyrate does not materially affect the circulation, whereas, as shown by Ehrmann (1913), large intravenous doses impair the cardiac action and cause a fall of the blood pressure, presumably on account of formation of β -hydroxybutyric acid and acetoacetic acid. Loewy and Ehrmann (1911) noted in rabbits a decrease of the carbon dioxide content of the blood during coma produced by the oral administration of 3.3 to 3.6 gm/kg. of sodium butyrate, which presumably was also produced by the formation of keto bodies. Fühner and Neubauer (1907) studied the *in vitro* hemolytic action of butyric acid, the minimum effective concentration being 0.0081 mol per liter.

According to Ehrmann (1911) the fatal dose of butyric acid with oral administration for rabbits is 3.6 to 3.7 gm/kg., and according to Dreyfus (1920) the toxicity for the same species is greatest with rectal administration, less marked with subcutaneous injection, and least with oral administration.

There are no reports on toxic effects of butyric acid for man.

MATERIAL SAFETY DATA SHEET

CELANESE CHEMICAL COMPANY, INC.

1250 WEST MOCKINGBIRD LANE

DALLAS, TEXAS 75247



CELANESE
CHEMICAL COMPANY, INC.

EMERGENCY
TELEPHONE NO: 806-665-5522

INFORMATION
TELEPHONE NO: 214-689-4000

REVISION
DATE: 11/79

IDENTIFICATION

PRODUCT NAME:

BUTYRIC ACID

CHEMICAL NAME:

Butyric Acid

CHEMICAL FAMILY:

Carboxylic Acids

FORMULA:

$\text{CH}_3(\text{CH}_2)_2\text{CO}_2\text{H}$

MOLECULAR WEIGHT:

88.10

SYNONYMS:

Butanoic Acid; Ethylacetic Acid; Propylformic Acid; Propanecarboxylic Acid

DEPARTMENT OF
TRANSPORTATION

HAZARD CLASSIFICATION
Corrosive

SHIPPING NAME

Butyric Acid

CHEMICAL ABSTRACT
REGISTRY NAME

Butanoic Acid

CHEMICAL ABSTRACT
REGISTRY NUMBER

107-92-6

PHYSICAL DATA

BOILING POINT, 760 mm. Hg.

163.5°C

FREEZING POINT

-6.3°C

SPECIFIC GRAVITY ($\text{H}_2\text{O} = 1$)
@ 20/20°C

.9597

VAPOR PRESSURE AT 20°C

less than 1 mm Hg

VAPOR DENSITY
($\text{AIR} = 1$)

more than 1

SOLUBILITY IN WATER
% BY WT.

Complete

PERCENT VOLATILES
BY VOLUME

100

EVAPORATION RATE
BuAc = 1

STATE

SOLID

LIQUID

X

GAS

APPEARANCE AND ODOR

Clear, colorless liquid with pungent, rancid odor.

HAZARDOUS INGREDIENTS

HAZARD

MATERIAL

%

CAS NO.

TLV^R

FIRE AND EXPLOSION HAZARD DATA

FLAMMABLE LIMITS IN AIR,
% BY VOLUME

LOWER
2.0

UPPER
10.0

FLASH POINT
(TEST METHOD)

166°F, TOC
161°F, TCC

EXTINGUISHING MEDIA Water spray, dry chemical, carbon dioxide, and alcohol foam are effective extinguishing agents for fires.

SPECIAL FIRE FIGHTING
PROCEDURES

Addition of water will reduce intensity of flames. If a leak or spill has not ignited, use water spray to disperse the vapor and to protect the personnel trying to stop the leak. Fire fighters should wear self-contained breathing apparatus and full protective clothing.

UNUSUAL FIRE AND
EXPLOSION HAZARDS

None.

REACTIVITY DATA

STABILITY

UNSTABLE

STABLE X

CONDITIONS TO AVOID

None.

INCOMPATIBILITY
(MATERIALS TO AVOID)

Strong oxidizing agents, strong alkalis.

HAZARDOUS COMBUSTION OR
DECOMPOSITION PRODUCTS

Thermal decomposition may produce carbon monoxide and carbon dioxide.

HAZARDOUS POLYMERIZATION

MAY OCCUR

WILL NOT OCCUR X

CONDITIONS TO AVOID

None.

HAZARD DATA		PERMISSABLE EXPOSURE LEVEL (OSHA STANDARD) None established.	
HOLD LIMIT VALUE) None established.			
OTHER			
EFFECTS OF EXPOSURE			
(SWALLOWING) ing to mucous membranes in concentrated form.			
(BREATHING) are very irritating to respiratory tract and mucous membranes.			
(CONTACT AND ABSORPTION) es severe damage to skin.			
(T) are highly irritating. Liquid produces severe damage.			
EFFECTS OF EXPOSURE			
currently known.			
AND FIRST AID PROCEDURES			
(T) Flush with water for at least 15 minutes. Contact a physician immediately.			
(CT) Wash area with water for at least 15 minutes. Contact a physician.			
(SWALLOWING) Make patient drink plenty of water to dilute acid concentration. Contact physician immediately.			
(BREATHING) Remove from contaminated area. If breathing has stopped, artificial respiration should be started and a physician called.			
OTHER HAZARDS			
PHYSICIAN			
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED			
Eliminate all sources of ignition. Only properly protected personnel should be permitted in area. Leaking containers should be removed to well-ventilated areas. Contain spill for salvage or disposal. Use of any dilution water should be closely controlled to minimize spill volume. Avoid run-off into storm sewers and ditches which lead to surface waterways. Advise authorities of spill.			
DISPOSAL METHOD			
Incinerator; biological treatment; landfill.			
RESPIRATORY PROTECTION (SPECIFY TYPE)		Use NIOSH approved organic vapor cartridge or canister respirator w/in use limitations of these devices; all other situations, self-contained breathing apparatus.	
EXPOSURE CONTROL	LOCAL EXHAUST Preferable.		
	MECHANICAL (GENERAL) Acceptable.		
	OTHER		
GLOVES ne or rubber gloves.		EYE PROTECTION Chemical safety goggles.	
PROTECTIVE EQUIPMENT			
Face mask, impervious boots, apron or clothing; eye bath and safety shower.			
ADDITIONAL PRECAUTIONS			
PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING			
Do not get in eyes, on skin, or on clothing. Avoid breathing vapors. Keep away from sparks and fire.			
ADDITIONAL PRECAUTIONS			

CRESOL

Cresylic acid

$\text{CH}_3\text{C}_6\text{H}_4\text{OH}$

All Isomers; Skin

TLV, 5 ppm ($\approx 22 \text{ mg/m}^3$)

Cresol, commercially a mixture of ortho, meta and para isomers derived from coal tar or petroleum, occurs as a colorless, yellowish or pinkish liquid with a phenolic odor. The molecular weight is 108.13 with a specific gravity between 1.030 and 1.038 at 25° C. It has a melting point from 11 to 35° C, a boiling range between 191 and 203° C and vapor pressures at 20° C of 0.25 (ortho), 0.15 (meta) and 0.11 mm Hg (para). The closed cup flash points of the isomers are 178° F for ortho and 187° F for both meta and para isomers. Cresol is soluble in alcohol, glycol and dilute alkalis. The National Formulary grade contains not more than 5% phenol.

It is used in making synthetic resins, as a disinfectant and fumigant, in photographic developers and explosives.

Little definitive toxicologic data on mixed cresols exist on which to base a TLV. Campbell⁽¹⁾ reported that mice appeared to tolerate single, brief exposures of saturated vapors of cresylic acid, but repeated exposures proved fatal. Smyth⁽²⁾ reported that rats survived an eight-hour exposure to substantially saturated cresol vapors at room temperature for eight hours. Neither investigator estimated the vapor concentration, but it was undoubtedly low, as Elkins⁽³⁾ reported that cresol is not sufficiently volatile to constitute a respiratory hazard under normal conditions. Elkins pointed out, however, that cresol is a strong dermal irritant and causes frequent dermatitis and that serious or even fatal poisoning may result if large areas of the skin are wet with cresol and not removed immediately.

Fairhall⁽⁴⁾ considered the toxicity of the mixed cresols to be somewhat less than that of phenol. Meta-cresol is somewhat less poisonous and less irritant than phenol, while ortho-cresol is more toxic and para-cresol is the most toxic of all three. These differences, however, are too small to be of any great practical importance. Hamilton and Hardy⁽⁵⁾ considered the action of cresol to be probably much the same as that of phenol.

Pathologic description of the changes induced by cresol are similar to those caused by phenol.⁽⁶⁾ These include irritation corrosion, hemorrhages, and destruction of the cellular cytoplasm of the gastrointestinal tract (from oral administration) kidney tubule damage, nodular pneumonia, and congestion of the liver with pallor and necrosis of the hepatic cells. Deichmann et al.⁽⁷⁾ reported rat oral LD₅₀'s to be 2.02 g/kg for the meta, 1.35 g/kg for the ortho and 1.8 g/kg for the para isomers.

In view of the lack of relevant quantitative toxicity data and in view of the closely analogous toxic action to phenol, a TLV of 5 ppm as a time-weighted average for mixed cresols is recommended.

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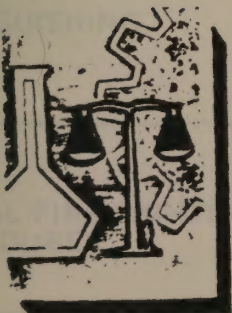
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NIOSH

CRITERIA FOR A RECOMMENDED STANDARD.... OCCUPATIONAL EXPOSURE TO

CRESOL

DHEW (NIOSH) Publication No. 78-133



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

MATERIAL SAFETY DATA SHEET

(Approved by U.S. Department of Labor "Essentially Similar" to Form OSHA-20)

n 11815

SECTION I

MANUFACTURER'S NAME Sherwin Williams Chemicals		EMERGENCY TELEPHONE NO. (312) 821-3216
ADDRESS (Number, Street, City, State, and ZIP Code) 1541 S. Champlain Avenue, Chicago, Ill. 60628		
CHEMICAL NAME AND SYNONYMS p-Hydroxy-toluene, p-cresol	TRADE NAME AND SYNONYMS p-cresol (CP 945)	
CHEMICAL FAMILY Phenol	FORMULA C ₇ H ₈ O	

SECTION II HAZARDOUS INGREDIENTS

MATERIAL	%	TLV (Units)
p-cresol	99	5ppm, 22mg/m ³ 29CFR 1910.1000 (rev. 7/1/76)
Corrosive to Skin (human data)		
Acute Dermal LD ₅₀ (rabbit) 301 mg/kg	Ind. Bio-Test/BIO-FAX	
Acute Oral LD ₅₀ (rats) 207 mg/kg		
Eye Irritant		
Primary Skin Irritant		
Acute Inhalation LC ₅₀ (rats) >0.71 mg/l		

SECTION III PHYSICAL DATA

BOILING POINT, 760 mm. Hg	395°F	FREEZING POINT	93°F
SPECIFIC GRAVITY (H ₂ O = 1)	1.022	VAPOR PRESSURE at 53°C	1 mm.Hg
VAPOR DENSITY (air = 1)	3.72	SOLUBILITY IN WATER, % by wt. at 20° C.	1.9
PERCENT VOLATILES BY VOLUME	NA	EVAPORATION RATE (Butyl Acetate = 1)	NA
APPEARANCE AND ODOR	Light-colored crystalline solid, sweet, tarry odor.		

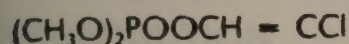
SECTION IV FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (test method)	187°F (CC)	AUTOIGNITION TEMPERATURE		1038°F	
FLAMMABLE LIMITS IN AIR, % by volume		LOWER	1.1 at 302°F	UPPER	1.0*
EXTINGUISHING MEDIA	Water fog or spray (may cause frothing), foam, dry chemical, CO ₂ .				
SPECIAL FIRE FIGHTING PROCEDURES	None				
UNUSUAL FIRE AND EXPLOSION HAZARDS	Slight explosion hazard in the form of vapor when exposed to heat or flame. Use water to cool fire-exposed containers.				

SECTION V HEALTH HAZARD DATA			
LD LIMIT VALUE 22 mg/m ³ 29 CFR 1910.1000 (rev. 7/1/76)			
OF OVEREXPOSURE ive action on skin and mucous membranes. Toxic by inhalation, skin absorption, and ving. May cause headache, dizziness, muscular weakness, breathing difficulty, matitis.			
CY AND FIRST AID PROCEDURES from further exposure. Wash contaminated area with copious amounts of water. s are involved, wash with a directed stream of water for 10 minutes. physician.			
SECTION VI REACTIVITY DATA			
	UNSTABLE		CONDITIONS TO AVOID
	STABLE	X	
ABILITY (Materials to avoid) ing Agents.			
US DECOMPOSITION PRODUCTS dioxide, carbon monoxide.			
US IZATION	MAY OCCUR		CONDITIONS TO AVOID
	WILL NOT OCCUR	X	
SECTION VII SPILL OR LEAK PROCEDURES			
BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED or shut down sources of sparks and flames. Immediately absorb with suitable absorbent. r to a covered, solid waste container. Wash down area with water until white n disappears.			
SPOSAL METHOD ration in accordance with local, state, and federal regulations. Discharge in ays or sewer system is not recommended.			
SECTION VIII SPECIAL PROTECTION INFORMATION			
ORY PROTECTION (Specify type) ed organic vapor cartridge respirator (e.g., MSA Comfo II, Welsh 7513)			
ION	LOCAL EXHAUST X-keep vapor concentrations below LEL		SPECIAL and TLV
	MECHANICAL (General)		OTHER
VE GLOVES gloves (e.g. Neoprene)		EYE PROTECTION Safety Glasses or masks.	
OTECTIVE EQUIPMENT tive coveralls or "rubberized" aprons.			
SECTION IX SPECIAL PRECAUTIONS			
ONS TO BE TAKEN IN HANDLING AND STORING t against physical damage. Store in cool, dry, well-ventilated location away from ea where fire hazard may be acute. Outside or detached storage preferred.			
ECAUTIONS all contact with skin, eyes, clothing. Do not take internally. Avoid breathing vapors. wear contaminated clothing. Clean up spill immediately.			

DICHLORVOS

2,2-Dichlorovinyl dimethyl phosphate; DDVP



Skin

TLV, 0.1 ppm ($\approx 1 \text{ mg/m}^3$)

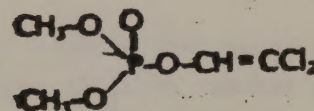
STEL, 0.3 ppm ($\approx 3 \text{ mg/m}^3$)

A nonflammable, amber liquid, dichlorvos has a molecular weight of 220.98 with a specific gravity at 25° C of 1.415. At 1.0 mm Hg pressure it boils at 84° C and has a vapor pressure of 0.01 mm Hg at 30° C. It is only slightly soluble in water (1%) and glycerine (0.5%), but is miscible with aromatic and chlorinated hydrocarbon solvents and alcohols. DDVP hydrolyzes at a rate of 3% per day in saturated aqueous solution at room temperature; at high pH or in boiling water it completely hydrolyzes in 1 hour.

Dichlorvos is used chiefly as an insecticide.

The acute toxicity for laboratory animals is rather high; the dermal LD₅₀ for male rats is 80 mg/kg,⁽¹⁾ indicating the need for a Skin notation. The LD₅₀ for oral, subcutaneous and intradermal routes in various species ranges from 12 to 135 mg/kg. The toxicology of DDVP has been reviewed for both inhalation and oral routes up to 1965 by FAO/WHO.⁽²⁾

Inhalation studies with laboratory animals have shown difficulty of achieving a lethal concentration in air with this compound because it is so readily absorbed on surfaces and hydrolyzed by moisture. Thus, it has been possible to kill animals (rats) by respiratory exposure only when their complete air supply was bubbled through the liquid insecticide directly into a small pyrex exposure chamber.⁽³⁾ Humans exposed at concentrations of dichlorvos varying from 0.14 to 0.33 mg/m³ for 30 minutes each hour, 10 hours a day for 14 days, showed no changes in cholinesterase or in a number of physiologic functions including airway resistance, visual acuity, accommodation or flicker fusion.⁽⁴⁾ On the other hand, when 28 human volunteers were exposed to dichlorvos by inhalation at a concentration of 1 mg/m³, single exposures of 7.5–8.5 hours resulted in plasma cholinesterase depression of 20–25%.⁽⁵⁾ As a result of these and similar studies, the joint Food and Agricultural and World Health Organizations has concluded that the no-effect level of DDVP is 0.033 mg/kg/day.⁽⁶⁾ This corresponds to a permissible exposure level of from 0.3 to 0.5 mg/m³ depending on the factor used for lung retention during an 8-hour day's exposure when 10 m³ of DDVP contaminated air are inhaled.



Moreover, Pukach *et al.*,⁽⁷⁾ in studies on pesticide workers handling dichlorvos, reported significant reduction was seen in blood cholinesterase as well as leukocytosis, neutrophilia and a decrease in lymphocytes and monocytes. These were back to normal at a 2 week follow-up following exposure. Symptoms of intoxication included weakness, headache, nausea, abdominal cramps, blurred vision, non-reactive pupils, tightness in the chest, salivation, sweating convulsions and coma.

The rapid degradation of dichlorvos, both in air and in the body, is probably responsible for the wide margin between that concentration which causes a detectable effect on the most sensitive indicator of exposure, plasma cholinesterase, and the concentration which produced noticeable symptoms of illness. Animal studies as well as human studies indicate such a wide margin between the concentration causing some plasma cholinesterase depression and the concentration likely to cause significant pathologic of biochemical changes that a TLV of 0.1 ppm and a STEL of 0.3 ppm are recommended. At the concentration of .1 ppm a 20% reduction in plasma cholinesterase may occur. This is without known physiologic significance, but does serve as an excellent monitoring device.

DDVP has been reported to be a weak mutagen by the *E. coli* strain WP₂ test.⁽⁸⁾

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Occupational Health Guideline for Dichlorvos

INTRODUCTION

This guideline is intended as a source of information for employees, employers, physicians, industrial hygienists, and other occupational health professionals who may have a need for such information. It does not attempt to present all data; rather, it presents pertinent information and data in summary form.

SUBSTANCE IDENTIFICATION

- **Formula:** $(CH_3O)_2POOCH=CCl_2$ or $C_4H_7Cl_2O_4P$
- **Synonyms:** DDVP; 2,2-dichlorovinyl dimethyl phosphate
- **Appearance and odor:** Colorless to amber liquid with a mild chemical odor.

PERMISSIBLE EXPOSURE LIMIT (PEL)

The current OSHA standard for dichlorvos is 1 milligram of dichlorvos per cubic meter of air (mg/m^3) averaged over an eight-hour work shift.

HEALTH HAZARD INFORMATION

- **Routes of exposure**
Dichlorvos can affect the body if it is inhaled, if it comes in contact with the eyes or skin, or if it is swallowed. It may enter the body through the skin.
- **Effects of overexposure**
 1. **Short-term Exposure:** After inhalation of dichlorvos, breathing and eye effects are the first to appear. These include tightness of the chest, wheezing, a bluish discoloration of the skin, small pupils, aching in and behind the eyes, blurring of vision, tearing, runny nose, headache, and watering of the mouth. After swallowing dichlorvos, loss of appetite, nausea, vomiting, abdominal cramps and diarrhea may appear within two hours. After skin absorption, sweating and twitching in the area of absorption may occur usually within 15 minutes to four hours. With severe intoxication by all routes, in addition to all the above symptoms, weakness, general-

ized twitching, and paralysis may occur and breathing may stop. In addition, dizziness, confusion, staggering, slurred speech, generalized sweating, irregular or slow heart beat, convulsions, and coma may occur.

2. **Long-term Exposure:** Repeated exposure to dichlorvos may make a person more susceptible to the effects of this and related chemicals. Repeated exposure to concentrations which are too small to produce symptoms after a single exposure may result in the onset of symptoms.

3. **Reporting Signs and Symptoms:** A physician should be contacted if anyone develops any signs or symptoms and suspects that they are caused by exposure to dichlorvos.

• Recommended medical surveillance

The following medical procedures should be made available to each employee who is exposed to dichlorvos at potentially hazardous levels:

1. Initial Medical Examination:

—A complete history and physical examination: The purpose is to detect pre-existing conditions that might place the exposed employee at increased risk, and to establish a baseline for future health monitoring. Persons with a history of reduced pulmonary function, convulsive disorders, or recent exposure to anticholinesterase agents would be expected to be at increased risk from exposure. Examination of the respiratory system, nervous system, cardiovascular system, and attention to the cholinesterase levels in the blood should be stressed. The skin should be examined for evidence of chronic disorders.

—Cholinesterase determination: Dichlorvos (DDVP) causes depressed levels of activity of cholinesterase in the serum and erythrocytes. The cholinesterase activity in the serum and erythrocytes should be determined by using medically acceptable biochemical tests prior to any new period of exposure.

2. **Periodic Medical Examination:** The aforementioned medical examinations should be repeated on an annual basis, with the exception of the cholinesterase determi-

These recommendations reflect good industrial hygiene and medical surveillance practices and their implementation will assist in achieving an effective occupational health program. However, they may not be sufficient to achieve compliance with all requirements of OSHA regulations.

which should be performed quarterly or at any time if overexposure is suspected or signs and symptoms of toxicity occur.

Summary of toxicology

Dichlorvos (DDVP) is an anticholinesterase agent; poisoning may occur from inhalation of the vapor or from skin absorption of the liquid, or from ingestion. Signs and symptoms of overexposure are caused by the inactivation of the enzyme cholinesterase, which results in the accumulation of acetylcholine at synapses in the nervous system, skeletal and smooth muscle, and salivary glands. The sequence of the development of toxic effects varies with the route of entry. The onset of signs and symptoms may occur promptly or may be delayed for up to 12 hours. After inhalation, respiratory and ocular effects are the first to appear, followed within a few minutes after exposure. Respiratory effects include tightness in the chest and wheezing due to bronchoconstriction and excessive bronchial secretions; laryngeal spasms and excessive salivation may add to the respiratory distress; cyanosis may also occur. Other effects include miosis, aching in and behind the eyes (attributed to ciliary spasm), blurring of distant vision, tearing, rhinorrhea, and frontal headache. After ingestion, gastrointestinal effects, such as anorexia, nausea, vomiting, abdominal cramps, and diarrhea may occur within 15 minutes to 2 hours. After skin absorption, localized sweating and muscular fasciculations in the exposed area occur usually within 15 minutes to 4 hours; skin absorption is somewhat greater at higher ambient temperatures and is increased by the presence of dermatitis. With severe intoxication by all routes, an accumulation of acetylcholine at the neuromuscular junctions causes weakness aggravated by exertion; involuntary twitchings, fasciculations, and eventually paralysis; the most serious consequence is paralysis of the respiratory muscles. Effects on the central nervous system include giddiness, confusion, ataxia, slurred speech, Cheyne-Stokes respiration, convulsions, coma, and loss of reflexes. The blood pressure may fall to low levels, and cardiac irregularities including complete heart block may occur; these effects may sometimes be reversed by establishing adequate pulmonary ventilation. Complete symptomatic recovery usually occurs within 1 week; increased susceptibility to the effects of anticholinesterase agents persists for weeks after exposure. Daily exposure to concentrations which are insufficient to produce symptoms following a single exposure may result in the onset of symptoms. Continued exposure may be followed by increasingly severe effects. In a study of 13 workers exposed for 12 months to an average concentration of 0.7 mg/m^3 , the erythrocyte cholinesterase activity was reduced by approximately 35%, and the serum cholinesterase activity was reduced by 60%; the results of other tests and of thorough medical examinations conducted at regular intervals were entirely normal.

CHEMICAL AND PHYSICAL PROPERTIES

• Physical data

1. Molecular weight: 221
2. Boiling point (1 mm Hg): 77 C (170 F)
3. Specific gravity (water = 1): 1.44
4. Vapor density (air = 1 at boiling point of dichlorvos): Not applicable
5. Melting point: Data not available
6. Vapor pressure at 32 C (90 F): 0.032 mm Hg
7. Solubility in water, g/100 g water at 20 C (68 F): 1 (approx).
8. Evaporation rate (butyl acetate = 1): Not applicable

• Reactivity

1. Conditions contributing to instability: None
2. Incompatibilities: None
3. Hazardous decomposition products: Toxic gases and vapors (such as hydrogen chloride gas, phosphoric acid mist, and carbon monoxide) may be released in a fire involving dichlorvos.
4. Special precautions: Dichlorvos will attack some forms of plastics, rubber, and coatings.

• Flammability

1. Not combustible

• Warning properties

1. Odor Threshold: No quantitative information is available concerning the odor threshold of dichlorvos.
2. Eye Irritation Level: Dichlorvos is not known to be an eye irritant.
3. Evaluation of Warning Properties: Since no quantitative information is available relating warning properties to air concentrations of dichlorvos, it is treated as a material with poor warning properties. The concentration in saturated air at 20 C could result in a significant exposure relative to the permissible exposure.

MONITORING AND MEASUREMENT PROCEDURES

• General

Measurements to determine employee exposure are best taken so that the average eight-hour exposure is based on a single eight-hour sample or on two four-hour samples. Several short-time interval samples (up to 30 minutes) may also be used to determine the average exposure level. Air samples should be taken in the employee's breathing zone (air that would most nearly represent that inhaled by the employee).

• Method

An analytical method for dichlorvos is in the *NIOSH Manual of Analytical Methods*, 2nd Ed., Vol. 5, 1979, available from the Government Printing Office, Washington, D.C. 20402 (GPO No. 017-033-00349-1).

RESPIRATORS

- Good industrial hygiene practices recommend that engineering controls be used to reduce environmental

concentrations to the permissible exposure level. However, there are some exceptions where respirators may be used to control exposure. Respirators may be used when engineering and work practice controls are not technically feasible, when such controls are in the process of being installed, or when they fail and need to be supplemented. Respirators may also be used for operations which require entry into tanks or closed vessels, and in emergency situations. If the use of respirators is necessary, the only respirators permitted are those that have been approved by the Mine Safety and Health Administration (formerly Mining Enforcement and Safety Administration) or by the National Institute for Occupational Safety and Health.

- In addition to respirator selection, a complete respiratory protection program should be instituted which includes regular training, maintenance, inspection, cleaning, and evaluation.

PERSONAL PROTECTIVE EQUIPMENT

- Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent repeated or prolonged skin contact with dichlorvos.
- Clothing contaminated with dichlorvos should be placed in closed containers for storage until it can be discarded or until provision is made for the removal of dichlorvos from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the dichlorvos, the person performing the operation should be informed of dichlorvos's hazardous properties.
- Non-impervious clothing which becomes contaminated with dichlorvos should be removed immediately and not reworn until the dichlorvos is removed from the clothing.
- Employees should be provided with and required to use splash-proof safety goggles where liquid dichlorvos may contact the eyes.

SANITATION

- Skin that becomes contaminated with dichlorvos should be immediately washed or showered with soap or mild detergent and water to remove any dichlorvos.
- Employees who handle dichlorvos should wash their hands thoroughly with soap or mild detergent and water before eating, smoking, or using toilet facilities.

COMMON OPERATIONS AND CONTROLS

The following list includes some common operations in which exposure to dichlorvos may occur and control methods which may be effective in each case:

Operation	Controls
Formulation and mixing for insecticidal application	Local exhaust ventilation; general dilution ventilation; personal protective equipment
Application on vegetables, animals, agricultural premises, and for outdoor fogging; insecticidal use of tablets, rubbing devices, resin strips, animal collars, dust on animals, animal buildings, restaurants, hospitals, and aircraft	Personal protective equipment
Manufacture of dichlorvos	Personal protective equipment

EMERGENCY FIRST AID PROCEDURES

In the event of an emergency, institute first aid procedures and send for first aid or medical assistance.

• Eye Exposure

If dichlorvos or dichlorvos mists get into the eyes, wash eyes immediately with large amounts of water, lifting the lower and upper lids occasionally. Get medical attention immediately. Contact lenses should not be worn when working with this chemical.

• Skin Exposure

If dichlorvos or dichlorvos mists get on the skin, immediately wash the contaminated skin using soap or mild detergent and water. If dichlorvos or dichlorvos mists soak through the clothing, remove the clothing immediately and wash the skin using soap or mild detergent and water. Get medical attention immediately.

• Breathing

If a person breathes in large amounts of dichlorvos, move the exposed person to fresh air at once. If breathing has stopped, perform artificial respiration. Keep the affected person warm and at rest. Get medical attention as soon as possible.

• Swallowing

When dichlorvos has been swallowed and the person is conscious, give the person large quantities of water immediately. After the water has been swallowed, try to get the person to vomit by having him touch the back of his throat with his finger. Do not make an unconscious person vomit. Get medical attention immediately.

• Rescue

Move the affected person from the hazardous exposure. If the exposed person has been overcome, notify someone else and put into effect the established emergency rescue procedures. Do not become a casualty. Under-

the facility's emergency rescue procedures and the locations of rescue equipment before the need

L, LEAK, AND DISPOSAL CEDURES

sons not wearing protective equipment and cloth-
ould be restricted from areas of spills or leaks until
up has been completed.

ichlorvos is spilled or leaked, the following steps
d be taken:

ntilate area of spill or leak.

ollect for reclamation or absorb in vermiculite, dry
earth, or a similar material.

ste disposal method:

orvos may be disposed of by absorbing it in
culite, dry sand, earth or a similar material and
sing in a secured sanitary landfill.

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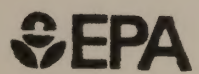
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RESPIRATORY PROTECTION FOR DICHLORVOS

Condition	Minimum Respiratory Protection* Required Above 1 mg/m ³
Particulate or Vapor Concentration	
10 mg/m ³ or less	Any supplied-air respirator. Any self-contained breathing apparatus.
50 mg/m ³ or less	Any supplied-air respirator with a full facepiece, helmet, or hood. Any self-contained breathing apparatus with a full facepiece.
200 mg/m ³ or less	A Type C supplied-air respirator operated in pressure-demand or other positive pressure or continuous-flow mode.
Greater than 200 mg/m ³ ** or entry and escape from unknown concentrations	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode. A combination respirator which includes a Type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode.
Fire Fighting	Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.
Escape	Any gas mask providing protection against organic vapors and particulates including pesticide respirators which meet the requirements of this class. Any escape self-contained breathing apparatus.

*Only NIOSH-approved or MSHA-approved equipment should be used.

**Use of supplied-air suits may be necessary to prevent skin contact while providing respiratory protection from airborne concentrations of dichlorvos; however, this equipment should be selected, used, and maintained under the immediate supervision of trained personnel. Where supplied-air suits are used above a concentration of 200 mg/m³, an auxiliary self-contained breathing apparatus operated in positive pressure mode should also be worn.



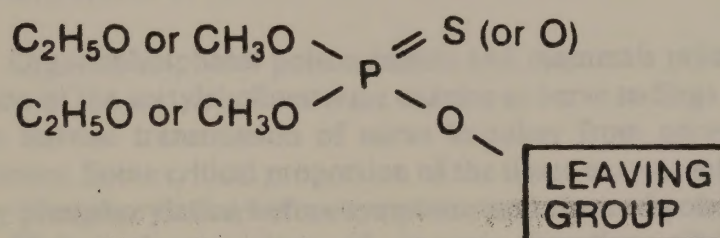
Recognition and Management of Pesticide Poisonings

Third Edition

Chapter 1

ORGANOPHOSPHATE CHOLINESTERASE-INHIBITING PESTICIDES

GENERAL CHEMICAL STRUCTURE



COMMON COMMERCIAL PESTICIDE PRODUCTS*

Highly toxic: tetraethyl pyrophosphate (TEPP), phorate (Thimet), disulfoton† (Di-Syston), fensulfothion (Dasanit), demeton† (Systox), terbufos (Counter), mevinphos (Phosdrin), methidathion (Supracide), chlormephos (Dotan, MC2188), sulfotepp (Bladafum, Dithione), chlorthiophos (Celathion), monocrotophos (Azodrin), fonofos (Dyfonate), prothoate (Fac), fenamiphos (Nemacur), phosfolan (Cyolane), methyl parathion (Dalf, Pennacap-M), schradan (OMPA), chlorfenvinphos (Birlane), ethyl parathion (Parathion, thiophos), azinphos-methyl (Guthion), phosphamidon (Dimecron), methamidophos (Monitor), dicrotophos (Bidrin), isofenphos (Amaze, Oftanol), bomyl (Swat), carbophenothion (Trithion), EPN, famphur, (Warbex, Bo-Ana, Famfos), fenophosphon (Agritox, trichloronate), dialifor (Torak), cyanofenphos (Surecide).

Moderately toxic: bromophos-ethyl (Nexagan), leptophos (Phosvel), dichlorvos (DDVP, Vapona), coumaphos (Co-Ral), ethoprop (Mocap), quinalphos (Bayrusil), triazophos (Hostathion), demeton-methyl† (Metasystox), propetamphos (Safrotin), chlorpyrifos (Lorsban, Dursban), sulprofos (Bolstar), dioxathion (Delnav), isoxathion (Karpfos), phosalone (Zolone), thiometon (Ekatin), heptenophos (Hostaquick), crotoxyphos (Ciodrin), cythioate (Proban), phencapton (G28029), DEF (De-Green, E-Z-off D), ethion, dimethoate (Cygon, De-Fend), fenthion (Baytex, Entex, Tiguvon, Spotton, Lysoff), dichlofenthion (Mobilawn), EPBP (S-Seven).

* These are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD₅₀ values (rat) less than 50 mg/kg; "moderately toxic" agents have LD₅₀ values in excess of 50 mg/kg.

† These organophosphates are systemic; i.e., they are taken up by the plant and translocated into foliage and sometimes into the fruit.

diazinon (Spectracide), phosmet (Imidan, Prolate), formothion (Anthio), profenofos (Curacron), naled (Dibrom), phenthoate, trichlorfon (Dylox, Dipterex, Neguvon), pyrazophos (Afugan, Curamil), fenitrothion (Agrothion, Sumithion), cyanophos (Cyanox), pyridaphenthion (Ofunack), propylthiopyrophosphate (Aspon), acephate (Orthene), merphos (Folex), malathion (Cythion), etrimfos (Ekamet), phoxim (Baythion), pirimiphosmethyl (Actellic), iodofenphos (Nuvanol-N), bromophos (Nexion), tetrachlorvinphos (Gardona, Rabon), temephos (Abate, Abathion).

TOXICOLOGY

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme at nerve endings. The enzyme is critical to normal transmission of nerve impulses from nerve fibers to innervated tissues. Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning are manifest. At sufficient dosage, loss of enzyme function allows accumulation of acetylcholine (the impulse-transmitter substance) at cholinergic neuroeffector junctions (muscarinic effects), and at skeletal myoneural junctions and in autonomic ganglia (nicotinic effects). Organophosphates also impair nerve impulse transmission in the brain, causing disturbances in sensorium, motor function, behavior, and respiratory drive. Depression of respiration is the usual cause of death in organophosphate poisoning. Recovery depends ultimately on generation of new enzyme.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. To a degree, toxicity depends on the rate at which specific organophosphates are metabolized in the body (principally by hydrolysis in the liver), thus limiting the amount of pesticide available to attack acetylcholinesterase enzyme in other tissues.

Many organophosphates readily undergo conversion from -thions to -oxons (replacement of sulfur by oxygen). In general, -oxons are much more toxic than -thions. This conversion occurs in the environment under the influence of sunlight and in the body, mainly by the action of liver microsomes. Ultimately, both -oxons and -thions are inactivated by hydrolysis at the ester linkage, yielding alkyl phosphates and phenols which are readily excreted. The hydrolysis products present little toxic hazard.

One to two days after organophosphate absorption, depending on the specific organophosphate, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by certain oxime antidotes. After this interval, the nature of the enzyme-phosphoryl bond changes, rendering the enzyme inactivation irreversible. New enzyme must then be generated.

Very rarely, organophosphate pesticides have produced a different type of neurotoxicity, consisting of damage to the myelin substance of peripheral nerves. This leads to a protracted peripheral neuropathy, characterized by numbness, pain, and weakness in the extremities, which persists for months or years. Organophosphates associated with these chronic illnesses have included

thion (Anthio), pro-
on (Dylox, Dipterex,
thion (Agrothion,
unack), propylthio-
(Folex), malathion
hosmethyl (Actellic),
orvinphos (Gardona,

rily by phosphoryla-
The enzyme is critical
fibers to innervated
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some whose acute toxic potential is low; i.e., there appears to be no relation-
ship between acute toxicity and the likelihood of a chronic neuropathic effect.
Particularly suspect as neurotoxic agents of this type are the phenylphospho-
nothioate series, cyanofenphos, EPN, leptophos, and EPBP.

Other unusual properties of specific organophosphates may render them
more hazardous than basic toxicity data suggest. By-products can develop in
long-stored malathion which strongly inhibit the hepatic enzymes operative in
malathion catabolism, thus enhancing its toxicity. Certain organophosphates
are exceptionally prone to storage in fat tissue, prolonging the need for an-
tidote when stored pesticide is released back into the circulation. It is possible
that other unrecognized factors modify the toxicity of organophosphates.

FREQUENT SYMPTOMS AND SIGNS OF POISONING

Symptoms of acute poisoning develop during exposure or within 12 hours
(usually within four hours) of contact. **HEADACHE, DIZZINESS, WEAK-
NESS, INCOORDINATION, MUSCLE TWITCHING, TREMOR, NAUSEA,
ABDOMINAL CRAMPS, DIARRHEA, and SWEATING** are common early
symptoms. Blurred or dark vision, confusion, tightness in the chest, wheezing,
productive cough, and **PULMONARY EDEMA** may occur. Incontinence, un-
consciousness and convulsions indicate very severe poisoning. **SLOW
HEARTBEAT**, salivation, and tearing are common. **TOXIC PSYCHOSIS**,
with manic or bizarre behavior, has led to misdiagnosis of acute alcoholism.
Slowing of the heartbeat may rarely progress to complete sinus arrest. **RESPI-
RATORY DEPRESSION** may be fatal. Continuing daily absorption of
organophosphate at intermediate dosage may cause an **INFLUENZA-LIKE
ILLNESS** characterized by weakness, anorexia, and malaise.

The very few individuals who have suffered peripheral neuropathy follow-
ing organophosphate exposure exhibited diverse clinical courses. Onset of
symptoms was generally slow, sometimes after an asymptomatic interval of
several days following exposure. Principal symptoms have been numbness,
tingling, pain and weakness of the arms and legs. Some recovered fully in a
few weeks; a few others experienced muscle atrophy, leaving a degree of
paresis and sensory loss.

CONFIRMATION OF DIAGNOSIS

CAUTION: If there are strong clinical indications of organophosphate
poisoning, treat patient immediately. **DO NOT WAIT** for
laboratory confirmation.

Depressions of plasma pseudocholinesterase and/or RBC acetylcholinester-
ase enzyme activities are the most satisfactory and generally available bio-
chemical indices of excessive organophosphate absorption. A minimum
amount of organophosphate must be absorbed to depress blood cholinesterase
activities, but activities are lowered by dosage considerably less than are re-
quired to cause symptomatic poisoning. The enzyme depression is usually ap-
parent immediately after, or within 12-24 hours of, significant absorption of

organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks; the RBC enzyme activity usually remains depressed longer, sometimes 1-3 months. Table 1 lists **APPROXIMATE LOWER LIMITS OF NORMAL FOR PLASMA and RBC CHOLINESTERASE ACTIVITIES** of human blood, measured by generally available methods. **LOWER LEVELS** usually indicate excessive absorption of a cholinesterase-inhibiting chemical. Whenever possible, comparison of the test sample with a pre-exposure value offers the best confirmation of organophosphate absorption: a depression of 25% or more is strong evidence of excessive absorption.

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemical inhibition. About 3% of individuals have a genetically determined low level of plasma cholinesterase. These persons are particularly vulnerable to the action of cholinesterase-inhibiting pesticides and to the drug succinylcholine, often administered to surgical patients. Patients with advanced liver disease, malnutrition, chronic alcoholism and dermatomyositis exhibit low plasma cholinesterase activities. A number of toxicants, notably carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines may reduce plasma pseudocholinesterase activity. The RBC acetylcholinesterase is less likely than the plasma enzyme to be affected by factors other than organophosphates. It is reduced, however, in certain conditions that damage the red cell membrane, such as hemolytic anemias.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to 48 hours thereafter. These analyses are useful in identifying the actual pesticide to which workers have been exposed. Alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than those required to depress cholinesterase activities.

Detection of intact organophosphates in the blood is usually not possible except after extreme exposures, such as ingestions of pesticide. Few organophosphates remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is extraordinary or the hydrolyzing liver enzymes are inhibited.

TREATMENT

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair.

1. Establish **CLEAR AIRWAY** by aspiration of secretions. Administer **OXYGEN** by mechanically assisted pulmonary ventilation. Improve tissue oxygenation as much as possible before administering atropine to minimize the risk of ventricular fibrillation.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly, if IV injection is not possible. Atropine protects the muscarinic end-organs from excessive concentrations of acetylcholine. It does not reactivate the

TABLE 1. *Approximate Lower Limits of Normal Plasma and Red Cell Cholinesterase Activities in Humans**

METHOD	PLASMA	RBC	WHOLE BLOOD	UNITS
Δ pH (Michel)	0.45	0.55		Δ pH per hr per ml
pH Stat (Nabb-Whitfield)	2.3	8.0		μ M per min per ml
ChE-tel (Pfizer)	40			ChE-tel units
A ChE-tel (Pfizer)		210		A ChE-tel units
BMC Reagent Set (Ellman-Boehringer)	1875		3000	mU per min per ml
1-Test Cholinesterase (EM Diagnostics)	3.6			Units per ml
Acholest Test Paper	>20			Minutes
Dupont ACA	< 8			Units per ml
Garry-Routh (Micro)			Male 7.8 Female 5.8	μ M-SH per 3 min per ml
Merckotest			3.0	Units per ml
GLC Method (Cranmer)	2.1	8.2		μ M per min per ml
Technicon	2.0	8.0		μ M per min per ml

* Because measurement technique varies among laboratories, more accurate estimates of minimum normal values are usually provided by individual laboratories.

cholinesterase enzyme. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off. Atropine is the ideal antidote for muscarinic manifestations; it is ineffective against nicotinic actions: muscle weakness and twitching, and respiratory depression.

In MODERATELY SEVERE poisoning:

Adult dosage, including children over 12 years: 0.4-2.0 mg repeated every 15 minutes until atropinization is achieved: tachycardia (pulse of 140 per minute), flushing, dry mouth, dilated pupils. Maintain atropinization by repeated doses for 2-12 hours or longer depending on severity of poisoning. Râles in the lung bases indicate inadequate atropinization. Miosis, nausea, bradycardia, and other cholinergic manifestations are also indicative.

Dosage for children under 12 years: 0.05 mg/kg body weight, repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated dosage of 0.02-0.05 mg/kg.

SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be

needed. Persons not poisoned or only slightly poisoned, however, may develop signs of atropine toxicity from such large dosages: **FEVER**, muscle fibrillations, and delirium are the main signs of atropine toxicity. If these signs appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily.

3. Draw a **BLOOD SAMPLE** for **PLASMA** and **RBC CHOLINESTERASE** analysis.
4. Administer **PRALIDOXIME** (Protopam®-Ayerst, 2-PAM) in cases of severe poisoning by organophosphate pesticides in which respiratory depression, muscle weakness and twitchings are severe. When administered early (usually less than 36 hours after poisoning) pralidoxime relieves the nicotinic effects of poisoning.

Note: Pralidoxime is of questionable value in poisonings by the cholinesterase-inhibiting carbamate compounds. (See Chapter 2).

Adult dosage (including children over 12 years): 1.0 gm intravenously at no more than 0.5 gm per minute.

Child's dose (under 12 years): 20-50 mg/kg (depending on severity of poisoning) intravenously, injecting no more than half the total dose per minute.

Dosage of pralidoxime may be repeated in 1-2 hours, then at 10-12 hour intervals if needed. In very severe poisonings, dosage rates may be doubled.

Note: *slow administration of pralidoxime is strongly recommended*, and may be achieved by administering the total dose in 250 ml 5% glucose solution over 30-60 minutes.

If intravenous injection is not possible, pralidoxime may be given by deep intramuscular injection.

CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed during and after pralidoxime injection.

5. **OBSERVE PATIENT CLOSELY** for at least 24 hours to insure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress and sometimes **PULMONARY EDEMA**) do not recur as atropinization wears off. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as 5-10 days, during which atropinization must be maintained. Rising levels of blood cholinesterase activity are a useful signal that atropine dosage can be tapered off by lengthening the intervals between doses. As dosage is reduced, the lung bases should be checked frequently for râles. If râles are heard, or if there is a return of miosis, bradycardia, sweating or other cholinergic signs, atropinization must be re-established promptly.
6. **BATHE** and **SHAMPOO** victim with soap and water if there is any chance that **SKIN** and **HAIR** are contaminated.

7. **IF PESTICIDE HAS BEEN INGESTED** in quantity sufficient to cause poisoning, empty the stomach and intestine.

A. **IF** victim is **ALERT** and respiration is not depressed, give **SYRUP OF IPECAC**, followed by 1-2 glasses of water to induce vomiting. Adults (12 years and over): 30 ml; children under 12 years: 15 ml.

CAUTION: **OBSERVE** victim closely **AFTER** administering **IPECAC**. If consciousness level declines, or if vomiting has not occurred in 15 minutes, proceed immediately to **INTUBATE** the stomach.

Following emesis, have victim drink a suspension of 30-50 gm **ACTIVATED CHARCOAL** in 3-4 ounces of water to limit absorption of toxicant remaining in the gut.

B. **IF** victim is **OBTUNDED** or respiration is depressed, empty stomach by **INTUBATION**, **ASPIRATION**, and **LAVAGE**, using isotonic saline or 5% sodium bicarbonate. Because many pesticides are dissolved in petroleum distillates, emesis and intubation of the stomach involve a serious risk that solvent will be aspirated, leading to chemical pneumonitis. For this reason:

(a). If victim is unconscious or obtunded and facilities are at hand, insert **ENDOTRACHEAL TUBE** (cuffed, if available) prior to gastric intubation.

(b). Keep victim's **HEAD BELOW LEVEL OF STOMACH** during intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to left.

(c). **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

After aspiration of gastric contents and washing of stomach, instill 30-50 gm of **ACTIVATED CHARCOAL** in 3-4 ounces of water through stomach tube to limit absorption of remaining toxicant.

C. **SAVE A SAMPLE** of emesis, or the initial gastric washings, for chemical analysis.

D. If bowel movement has not occurred in 4 hours, and if patient is fully conscious, give **SODIUM SULFATE**, 0.25 gm/kg, in 1-6 ounces water, as a cathartic. Magnesium sulfate and citrate are equally suitable at similar dosage if renal function is adequate. Retained magnesium may depress CNS function.

8. **DO NOT** give morphine, aminophylline, phenothiazines, reserpine, furosemide, or ethacrynic acid in poisonings by organophosphates.

9. Give adrenergic amines **ONLY** if there is a specific indication, such as marked hypotension.

10. Rarely, in severe organophosphate poisonings, **CONVULSIONS** occur which are unresponsive to atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia, or mixed poisoning. **DIAZEPAM** (Valium), 5-10 mg for adults, 0.1 mg/kg for children under 6 years or 23 kg is probably the safest and most reliable anticonvulsant to use under these circumstances. Give **SLOWLY** (no more than half the total dose per minute) intravenously. Severe protracted convulsions may require additional medication, as suggested in the chapter on *Solid Organochlorine Pesticides*.

CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed; to intubate the trachea, if laryngospasm occurs; and to counteract hypotensive reactions.

11. Persons who have been clinically poisoned by organophosphate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80 percent of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels (Table 1) before the patient is returned to a pesticide-contaminated environment.
12. **DO NOT** administer atropine or pralidoxime prophylactically to workers exposed to organophosphate pesticides. It is neither practical nor medically sound to do so.

National Cancer Institute

CARCINOGENESIS

Technical Report Series

No. 10

1977

**BIOASSAY OF
DICHLORVOS
FOR POSSIBLE CARCINOGENICITY**

CAS No. 62-73-7

NCI-CG-TR-10

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

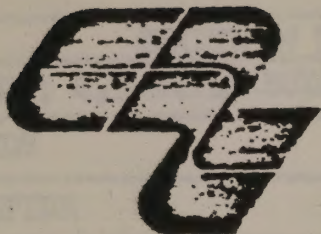


SUMMARY

A bioassay for the possible carcinogenicity of technical-grade dichlorvos was conducted using Osborne-Mendel rats and B6C3F1 mice. The test material was administered in the diet at two concentrations for 80 weeks to groups of 50 animals of each species and sex. The test animals were held for observation, and surviving rats were killed at 110-111 weeks and surviving mice at 92-94 weeks from initiation of the study. Initial doses in both species were not well tolerated and they were lowered after a few weeks. Time-weighted average doses for both males and females were 150 and 326 ppm for rats and 318 and 635 ppm for mice. The matched controls consisted of 10 rats of each sex and 10 mice of each sex; the pooled controls consisted of 60 rats of each sex, 100 male mice, and 80 female mice. All surviving rats were killed at 106 to 109 weeks; surviving mice, at 92 to 94 weeks.

After the doses were reduced, no toxic signs directly attributable to the compound were observed. However, average weights of high-dose animals were slightly depressed. Survival was not dose-related in either species. Microscopic study of the tissues of treated animals and matched and pooled controls revealed no statistically significant increase in the incidence of tumors attributable to exposure to dichlorvos in either animal species. The significance of the three esophageal tumors in male and female mice and of malignant fibrous histiocytomas in male mice is unclear and there is insufficient evidence to indicate they were associated with dichlorvos treatment. Thus under the conditions of this study, dichlorvos was not demonstrated to be carcinogenic.

ownZellerbach
mical Products Division

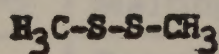
**DIMETHYL DISULFIDE**

Regulatory Agency Information
TSCA - DOT - OSHA

S, WASHINGTON 20007

323-1

July, 1977

PRODUCT INFORMATION BULLETIN

DIMETHYL DISULFIDE; DMS

Toxic Substances Control Act Registration

CAS Name: Disulfide, Dimethyl

CAS Registry Number: 624-92-0

Department of Transportation Regulation

DOT Hazardous Materials Regulations 49 CFR

Hazard Class: Flammable Liquid

Proper Shipping Name: Flammable Liquid, NOS
(Dimethyl Disulfide)

Shipping Classification: Flammable Liquid

MATERIAL SAFETY DATA SHEET

SECTION I

Name	DMETHYL DISULFIDE; 2,3-DITHIABUTANE
	METHYL DISULFIDE, DMDS
	DMDS; DIMETHYL DISULFIDE
Family	ALIPHATIC DISULFIDE
	$H_3C-S-S-CH_3$; $C_2H_6S_2$

Crown Zellerbach Corporation
Chemical Products Division
Camas, Washington 98607
Phone: (206) 834-4444

SECTION II - N.A.

SECTION III - PHYSICAL DATA

Point	109 °C	229 °F	Melting Point	-85 °C	-121 °F
Pressure		22 mm Hg	Specific Gravity ($H_2O = 1$)	1.0644	
Density (1)	3.24		Evaporation Rate (Bu acetate = 1)	1	
Solubility in Water			Molecular Weight	94.19	
Weight	Slight				
Solubility in Solvents	Soluble in most common organic solvents.				
Color and Odor	Light yellow liquid; sharp unpleasant odor.				

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

Flash Point (Method) (°C)	24 °C	76 °F	Autoignition Temp.	°C	°F
Explosion Limits in Air (% by Vol.)			Lower	Upper	
Extinguishing	Water fog, foam, alcohol foam				
Fire Procedures	Treat as burning, volatile petroleum product.				
Fire Hazard	SO ₂ is present in combustion gases.				

SECTION V - HEALTH HAZARD DATA

Permissible Exposure Limit (TLV)	Not Determined	Oral (rats): 813 mg/kg LD50 Dermal (rats): 10,200 mg/kg
Irritation		Skin Irritation
	Vapor LC50 (rats): 4.8 mg/L air	
Health Effects of Exposure	Unknown	

Equivalent in Content to OSHA-20

SECTION V - HEALTH HAZARD DATA (Cont'd)

act	Wash thoroughly with running water for about 15 minutes.
act	Wash thoroughly with running water.
on	Remove from contaminated area and give artificial respiration and oxygen if needed.
n	If swallowed, induce vomiting. Call a physician.

SECTION VI - REACTIVITY DATA

(Thermal c.)	Stable	X	Conditions to Avoid	
us	Unstable		Conditions to Avoid	
ization	May Occur		Conditions to Avoid	
stability	Will Not Occur	X	Conditions to Avoid	
ls to Avoid				
us Decom-Products	Oxides of sulfur			

SECTION VII - SPILL OR LEAK PROCEDURES

ons if is Re-r Spilled	Wash down with water. Minor DMDS spills can be rendered nonflammable and nonodorous by spraying with <u>liquid</u> hypochlorite solutions (e.g. Purex, Chlorox).
Disposal	

SECTION VIII - SPECIAL PROTECTION INFORMATION

ection	Safety glasses or goggles. Use face shield if needed.
ory on	Use respirator with organic vapor canister if needed.
on	Protective gloves
on	Good exhaust ventilation where vapors or mist present.

SECTION IX - SPECIAL PRECAUTIONS

g and	Keep containers closed. Protect from sparks, open flame, or extreme heat.
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SECTION X - SHIPPING REGULATIONS

subject to Hazardous Materials Regulations as a Flammable Liquid. Shipping papers labels must contain the proper name (Flammable Liquid, NOS, Dimethyl disulfide), classification (Flammable Liquid), a caution against breathing vapors, and name and address of the shipper.

The subacute inhalation toxicity of 103 industrial chemicals

J. C. F. J. C.

Imperial Chemical Industries Limited, London Research Department, London, England

Comp. J. C. (1976) and J. C. (1977) and J. C. (1978) The subacute inhalation toxicity of 103 industrial chemicals. The subacute toxicity of 103 substances has been studied by means of a standard method in a species representative of the human population. The results of these studies are presented in this bulletin. The results are presented in a form which is suitable for use by the designer of new plants and by the manufacturer of new products.

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- 75 Acrylonitrile, 10
- 76 Acrylonitrile, 10
- 77 Acrylonitrile, 10
- 78 Acrylonitrile, 10
- 79 Acrylonitrile, 10
- 80 Acrylonitrile, 10
- 81 Acrylonitrile, 10
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- 83 Acrylonitrile, 10
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- 85 Acrylonitrile, 10
- 86 Acrylonitrile, 10
- 87 Acrylonitrile, 10
- 88 Acrylonitrile, 10
- 89 Acrylonitrile, 10
- 90 Acrylonitrile, 10
- 91 Acrylonitrile, 10
- 92 Acrylonitrile, 10
- 93 Acrylonitrile, 10
- 94 Acrylonitrile, 10
- 95 Acrylonitrile, 10
- 96 Acrylonitrile, 10
- 97 Acrylonitrile, 10
- 98 Acrylonitrile, 10
- 99 Acrylonitrile, 10
- 100 Acrylonitrile, 10

The subacute inhalation toxicity of 109 industrial chemicals

J. C. GAGE

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Gage, J. C. (1970). *Brit. J. industr. Med.*, 27, 1-18. The subacute inhalation toxicity of 109 industrial chemicals. The inhalation toxicity of 109 substances has been studied by exposing experimental animals to known concentrations in air for periods of about three weeks. The toxic properties of these substances are reviewed in relation to the effects of similar compounds on animals and on man. Provisional operational limits are suggested to assist in the design of new plant and in the establishment of codes for safe manufacturing practice.

Most serious occupational diseases arising from exposure to chemicals are caused by an attack on, or absorption through, the respiratory tract. On occasion such effects can be predicted from oral or parenteral administration of the chemical to experimental animals, but, in general, if a substance presents an inhalation risk, it is preferable to undertake a direct investigation by exposing animals to known concentrations in air. This survey covers the work on inhalation toxicity which has been undertaken over a period of 20 years in a laboratory engaged in the study of the toxic properties of chemicals used in industry.

All of the samples investigated for inhalation toxicity over this period were submitted by the manufacturing divisions of ICI Ltd.; they averaged about 40 a year. Not all of these have been included in this survey. Some were of too indeterminate a composition, such as still residues; some were proprietary products whose formulation was uncertain; for some the investigation was never completed for a variety of reasons; for a few, publication has been restricted for commercial or other considerations.

The aim of these investigations has been to provide information to aid in plant design and in the establishment of safety precautions to prevent occupational disease when the materials are produced or used in manufacturing operations. The experimental

results have led to a decision on whether the compound may be handled without special precautions other than those demanded by sound manufacturing practice, whether exhaust ventilation should be installed or whether other features in plant design are required to prevent excessive exposure. The results have also enabled a prediction of the effects likely to be encountered in man from brief or repeated over-exposure, and have provided guidance on treatment to a works medical officer confronted with an accident or with a failure to apply the recommended safety precautions.

The compounds investigated are indexed below in alphabetical order.

1-Acetyl- γ -butyrolactone, 10
Acrylic acid, 6
Acrylyl chloride, 14
Adipic acid, 6
2-Aminobutan-1-ol, 10
2-Aminomethyl-3, 4-dihydropyran, 11
Bis-2-chloro-1-methylethyl ether, 6
Bis-2-ethoxyethyl ether, 6
2,2-Bis-*p*-hydroxyphenylpropane, 14
Bis-2-methoxyethyl ether, 6
Bis-3-methylbutyl peroxydicarbonate 11
Bispentafluorosulphur oxide, 13
(2-Bromoethoxy) benzene, 7
5-Bromopentan-2-one, 6

- 2-*t*-Butoxyethanol, 5
s-Butylamine, 9
t-Butyl peracetate, 11
t-Butyl peroxyphthalate, 11
n-Butyraldehyde, 6
 Cetostearyl methacrylate, 8
 Chloroacetonitrile, 10
 6-Chlorododecafluorohexylsulphur pentafluoride, 14
 2-Chloroethylsulphur pentafluoride, 13
 1-Chloronaphthalene (technical), 8
 4-Chloro-octafluorobutylsulphur pentafluoride, 13
 Chloropentafluorobenzene, 7
 1-Chloropropan-2-ol, 5
 2-Chloropropane, 6
 2-Chlorotetrafluoroethylsulphur pentafluoride, 13
 Cumene α -hydroperoxide, 11
N-2-Cyanoethylamine, 10
 Decahydronaphthalene, 5
 1,6-Diaminohexane, 9
 Dichlorobutenes (mixed isomers), 7
 1,1-Dichloroethene, 7
 1,3-Dichlorotetrafluorobenzene, 7
 α -Dicyclopentadiene, 4
 1-Diethylaminopentan-2-one, 10
 Diethylenetriamine, 10
OO-Diethyl phosphorochloridothionate, 12
 Dimethoxymethane, 5
 2-Dimethylaminoethyl methacrylate, 8
 3,6-Dimethyl-1,2-benzisoxazole, 11
 Dimethyl carbonate, 9
 Dimethyl disulphide, 13
 3,5-Dimethylmorpholine, 11
 Dinonylamine, 9
 Diphenyldimethoxysilane, 12
 Dipropionyl peroxide, 11
 Di-*s*-butylamine, 9
 Divinyl disulphide, 13
 Dixyl disulphide, 13
 Ethyl chloroformate, 9
 Ethyl 3-chlorophenylformimidate, 14
 2-Ethylhexyl acrylate, 8
 2-Ethylhexyl methacrylate, 8
 2-Ethyl-2-hydroxymethylpropane-1, 3-diol, 5
 Ethyl *t*-butyl peroxyoxalate, 11
N-Formylpiperidine, 10
 Glycol dimethacrylate, 8
 Hexachlorobutadiene, 7
 Hexafluorobenzene, 7
NN-Hexamethyleneadipamide, 14
 2-Hydroxyethyl methacrylate, 8
 2-Hydroxypropyl methacrylate, 8
 4-Hydroxytetrahydropyran, 11
 Iron pentacarbonyl, 14
 Isobutoxyethene, 5
 Isobutyraldehyde, 6
 Iso-octanol, 5
 2-Isopropoxyethanol, 5
 Isopropyl chloroformate, 9
 Lauryl mercaptan, 13
 Lauryl methacrylate, 8
 Methacrylic acid, 6
 2-Methoxy-3,4-dihydropyran, 11
 Methoxyethene, 5
 2-Methylbenzoxazole, 10
 2-Methylbuta-1,3-diene, 4
 Methyl chloroformate, 8
 2-Methyl-1,3-dioxolan, 10
 Methyl isothiocyanate, 8
 Methyl nitrite, 9
 Methyl salicylate, 8
 2-Methylthiazole, 10
 Nonylamine, 9
 Octyl methacrylate, 8
 Pentachloropyridine, 10
 Phosphorus tri-isocyanate, 12
 Propionaldehyde, 6
n-Propyl cyanide, 10
N-Propylethylideneamine, 14
 Silicon tetrafluoride, 12
 Silicon tetraisocyanate, 12
 Sulphur chloride pentafluoride, 13
 Sulphur dichloride, 12
 3a,4,7,7a-Tetrahydro-4,7-methanoindene, 4
 Tetramethylsilane, 12
 Tributylamine, 9
 Tributyl phosphite, 12
 1,2,4-Trichlorobenzene, 7
 Trichloromethylsulphenyl chloride, 13
 1,3,5-Trichlorotrifluorobenzene, 7
 Trimethoxyboroxine, 14
 1, 2, 4-Trimethylbenzene, 5
 Trinonylamine, 9
 Triisopentafluoroethylmethanol, 5
 1, 1, 1-Tris(hydroxymethyl)propane bicyclic phosphite, 12
 Vinyl acetate, 8
 Vinylsulphur pentafluoride, 13

Methods and materials

Samples investigated

The samples submitted by ICI Divisions were prepared in either the Research Department or an experimental plant, or were taken from full-scale production. The size of the sample available determined to some extent the scale of the experimental work. Few of the samples could be described as pure chemicals; they were not fractionated before use as the toxicological properties of the materials as supplied were relevant to these investigations. Where the sample was known to contain a considerable admixture of other components, this information is included in the Results section.

Design of exposure chambers

In all of these experiments the animals have been exposed to dynamic atmospheres, that is, to atmospheres continuously generated and passed through the exposure chamber. The design of exposure chamber has varied with the number of animals involved and with the nature of the substance under investigation. For groups of four or fewer rats a glass desiccator, containing wire mesh partitions to separate the animals, was used. Larger numbers, up to eight rats, were exposed in the chamber described elsewhere (Gage, 1959); usually the inner Perspex chamber of that design was replaced by a glass cylinder, 30 cm diameter and 25 cm high. For atmospheres containing particulate matter a chamber with a more pyramidal top (Gage, 1968) was used.

Generation of the test atmospheres

The air used for the atmospheres was filtered, dried to a relative humidity of less than 10%, and supplied at a line pressure of 1 atm (1.013×10^5 Nm⁻²). In the Results section, the methods used to prepare the atmospheres are indicated by letters in parentheses which refer to the following list. The letter is followed by any information relating to the particular experiment.

- A A nearly saturated vapour obtained by passing air through a liquid contained in a bubbler with a sintered glass air-distributor disc. The volume of the liquid was usually 10-20 ml and, if the size of the sample available permitted, it was replaced daily. Unless otherwise stated, the bubbler was maintained in a water-bath at room temperature, about 20°C.
- B A nearly saturated vapour obtained by passing air through a column of a granular solid. If the sample supplied was a fine powder, it was dispersed on the surface of granular kieselguhr.
- C An atmosphere prepared by methods A or B and diluted to a known extent with clean air.
- D A vapour concentration by injecting a liquid at a known rate into a metered stream of air by means of a controlled fluid-feed atomizer (Gage, 1953). For concentrations much less than 100 ppm a solution of the liquid in a toxicologically inert solvent was used. For very volatile liquids the syringe was cooled in an ice-water bath.
- E A metered stream of a gas or vapour from a cylinder was diluted with a metered stream of air. The diluted gas was passed through a jet to produce efficient mixing by turbulence.
- F A gas or vapour contained in a large polyethylene bag at atmospheric pressure was introduced into a metered air stream at a known rate by means of a peristaltic pump (Watson Marlow).
- G A powdered solid injected into a metered air stream at a known rate by the apparatus described by Byers and Gage (1961).
- H A condensed fume prepared by passing an aerosol obtained by methods D or G through a well-insulated cylindrical electric furnace located in the central tube of the exposure chamber. The furnace was heated to a temperature sufficiently high to volatilize the substance, which on cooling condensed to a fume.
- I A method was devised for the continuous generation of methyl nitrite, which is too unstable to be isolated and stored. A solution of hydrochloric acid in methanol was injected at a known rate on to a mixture of equal parts of sodium nitrite and anhydrous sodium sulphate. In the presence of excess methanol the rate of addition of hydrochloric acid defined the rate of liberation of methyl nitrite. The vapour diffused through a sintered glass plate into a metered air stream.

Measurement of concentration

The nearly saturated concentration prepared by methods A and B was estimated by weighing the sample before and after the day's run, and relating the weight loss to the volume of air passing. This concentration, expressed in milligrammes per litre, was converted to parts per million on the assumption that the sample was pure.

Both of these estimates are only approximate; this applies particularly to materials of low volatility and to impure samples when the more volatile fraction may evaporate first. For these reasons method D was usually preferred for such materials.

With the other methods the concentrations have usually been those calculated from the known rate of introduction of the substance into the air stream. In some experiments the concentration was checked by direct analysis of the atmosphere and was found to be within 10% of the expected value. A direct determination was always made when the method could not give a reliable indication of concentration, as with aerosols or organic peroxides. Concentrations determined by analysis are indicated by a superscript letter which refers to the following list.

- a Gas-liquid chromatography. A Pye 104 instrument with a flame ionization detector was used. The column was 5 ft by 1/8 in, filled with 60-80 mesh Celite coated with SE30. The temperature of the column was maintained at about 20% below the boiling point of the liquid. A sample of the atmosphere was injected directly into the N₂ carrier gas by means of a gas sampling valve (0.5-10 ml).
- b Peroxides by iodometry. A measured volume of the air was passed through a 1% w/v aqueous potassium iodide solution, and the liberated iodine was measured absorptometrically at 425 nm.
- c Peroxides by oxidation of ferrous thiocyanate. A 50-ml sample of the air was collected in a large glass syringe containing 10 ml ferrous thiocyanate reagent (100 ml 0.5% w/v ammonium thiocyanate, 1 ml 6 N sulphuric acid, 0.1 g ferrous ammonium sulphate, 100 ml water, prepared freshly each day). The syringe was shaken for 5 minutes and the ferric thiocyanate concentration was measured absorptometrically at 460 nm.
- d Titration. A measured volume of the air was passed through water (sulphur dichloride) or 10% v/v aqueous ethanol (adipic acid) and the absorbed acid was titrated with sodium hydroxide solution.
- e Methyl nitrite. A measured volume of the air was passed through 10 ml reagent (0.1 g chloroaniline, 10 ml N HCl, acetic acid to 1 litre); 2 ml 1% aqueous N-(1-naphthyl)ethylenediamine dihydrochloride was added, and after 15 minutes the absorbance was measured at 550 nm.

Design of the experiments

Alderley Park specific-pathogen-free rats with an average weight of 200 g were used in most of these experiments. They were maintained in the exposure chamber for periods of up to 6 hours, and between repeated daily exposures they were returned to their cages where food and water were freely available. In the initial experiments the concentrations were selected to produce, if possible, acute effects after short exposures. Thereafter the exposure period was extended and the concentration lowered until the animals could survive 6-hour exposures, five days a week, for up to four weeks. With liquids, the vapour pressure limited the range of concentrations which could be tested in these acute and subacute experiments. The rats were weighed each morning, and their conditions and behaviour were recorded throughout the exposure period. Urine was collected overnight

after the last exposure day for biochemical tests. The animals were left overnight with food and drink. On the following day the rats were anaesthetized with halothane and partially exsanguinated by heart puncture for haematological tests. After a gross examination of the organs, the lungs were inflated with formol-saline and immersed in the same fixative. The following organs were also taken for microscopical examination after fixation in formol-corrosive: lungs, liver, kidneys, spleen, and adrenals; and occasionally heart, jejunum, ileum, and thymus.

If at any stage effects were observed which could be attributed to the exposure, the experiment was repeated with progressively lower concentrations until a concentration was reached which was without effects on the animals. At intervals of about two months, batches of control rats were maintained in a chamber for the exposure period, in order to check the characteristics of the colony.

Results

Presentation of experimental results

Where practicable, the chemical name used is that recommended by the International Union of Pure and Applied Chemistry (IUPAC) classification. This is followed in brackets by any other name in common usage. Where the IUPAC name is little used, as with methacrylic acid, the widely used name appears first, followed by the systematic name. Any information on purity is included. A structural formula is given. The physical state and the melting or boiling points (where known) are stated.

Details of the experiments undertaken and the results obtained are presented according to the following scheme:

Atmospheric concentration and method of generation; number, sex, and species of animals; number and duration of exposures; clinical observations; autopsy.

The following annotations explain the conventions used in this presentation.

Atmosphere The measured or calculated concentration followed in parentheses by a letter indicating the method of generating the atmosphere and any special details. A superscript letter indicates the method used for determining the concentration. These letters refer to procedures detailed in the Methods section. Unless otherwise stated, the concentrations were dilutions of a vapour or a gas. With 'saturated' atmospheres, the concentration in brackets is that estimated from the weight loss, unless otherwise indicated.

Clinical observations The following descriptive terms have been used: *nose irritation*, sneezing

progressing with increasing severity to a nasal discharge and a bloody exudate; *eye irritation*, eyes closed, progressing to lachrymation; *respiratory difficulty*, rapid shallow breathing progressing to laboured and slow breathing; *lethargy*, less than normal activity and a lower response to noise; *hypersensitive* or *unresponsive*, an increased or diminished reaction, respectively, to noise and handling; *incoordination*, unsteady movements, *staggering gait*; *no toxic signs* implies that the animals remained in good condition. In most experiments blood and urine tests were made at the lower concentrations, and any abnormal results are indicated. The urine tests included specific gravity, pH, reducing sugars, bilirubin, and protein. The blood tests included haemoglobin (Hb) concentration, packed cell volume, mean corpuscular Hb content, a white and differential cell count, a platelet count, clotting function, and the concentration of urea sodium, and potassium. Control tests for the haematological examination were made on the group of animals before exposure. **Autopsy**—no comment on the gross pathology indicates that the organs appeared normal. Comment after (*histol.*) indicates effects seen on microscopical examination of the tissues. *Organs normal* indicates that these examinations revealed no changes which could be attributed to the treatment.

Hydrocarbons

2-Methylbuta-1,3-diene $\text{CH}_3\text{CH}=\text{CMeCH}_3$
[isoprene]

liq. b.p. 34°C

6000 ppm (D, cooled): 2M 2F rats: 6 × 6-hr exposures: no toxic signs: autopsy, lungs slightly congested, (*histol.*) organs normal

1670 ppm (D, cooled): 2M 2F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal

3a,4,7,7a-Tetrahydro-4,7-methanoindene
[α-Dicyclopentadiene]

solid m.p. $25-30^\circ\text{C}$, b.p. 170°
(decomp.)

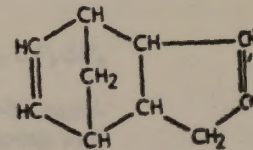
2500 ppm (D, pet. ether): 2M

2F rats: 1 × 1-hr exposure: eye and nose irritation, dyspnoea, narcosis, 1 died later: autopsy (*histol.*) lungs, liver and kidneys congested

1000 ppm (D, pet. ether): 2M 2F rats: 1 × 4-hr exposure: eye and nose irritation, dyspnoea, muscular incoordination, tremors, hypersensitive all died later: autopsy, lungs congested, (*histol.*) lungs, liver, and kidneys congested

250 ppm (D, pet. ether): 2M 2F rats: 10 × 6-hr exposures: 1 died after 2nd exposure, survive lost weight, nose irritation, dyspnoea, lethargy, tremors, hypersensitive, blood tests normal: autopsy organs normal

100 ppm (D, pet. ether): 4M 4F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal



1,2,4-Tris.
[pseudocumene]
liq. b.p.
Saturated
12
respir.
increased
normal
1000 ppm
initial
normal
Decahydro
[decalin]
liq. b.p.
1000 ppm
tremors
congested
200 ppm
toxic signs

Alcohols

Iso-octanol
 C_8H_{18}
liq. b.p.
Saturated
exposure

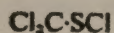
2-Isopropyl
[isopropyl]
liq. b.p.
1000 ppm
initial
porphyria
reticulated
autopsy
congested
300 ppm
slight
autopsy
100 ppm
no toxic signs

2-1-Butoxy
[t-butyl glycol]
liq. b.p.
Saturated
1 × 5-hr
35-50%
250 ppm
initial
MCHC
100 ppm
no toxic signs
from inorganic
organs normal
50 ppm (1)
100 ppm
20 ppm (1)
toxic signs

Tris(pentafluorophenyl)
[trifluoromethyl]
liq. b.p. 105°C

tures: 4M 4F rats: no toxic signs: autopsy, organs normal

Trichloromethylsulphenyl chloride



liq. b.p. 148-9°C

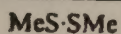
100 ppm (D): 4M rats: 1 × 1-hr exposure: severe respiratory difficulty, all died: autopsy (histol.) lung oedema

10 ppm (D, acetone): 4M rats: 1 × 6-hr exposure: lethargy, respiratory difficulty, 3 died later: autopsy (histol.) lung oedema

2 ppm (D, acetone): 4M rats: 20 × 6-hr exposures: initial respiratory difficulty: autopsy, lungs congested

0.5 ppm (D, acetone): 4M 4F rats: 20 × 6-hr exposures: no toxic signs: autopsy, organs normal

Dimethyl disulphide

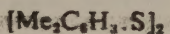


liq. b.p. 112°C

250 ppm (D): 2M 2F rats: 13 × 6-hr exposures: lethargy, respiratory difficulty, low weight gain: autopsy, organs congested

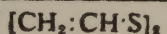
100 ppm (D): 2M 2F rats: 20 × 6-hr exposures: no toxic signs: autopsy, organs normal

Diethyl disulphide (solution in mineral oil contained about 40% with other sulphides)



Saturated [3.5 µg/litre]: 4F rats: 15 × 7-hr exposures: no toxic signs: autopsy, organs normal

Divinyl disulphide



liq. b.p. 86°C

480 ppm (D): 2M 2F rats: 1 × 4.5-hr exposure: eye and nose irritation, respiratory difficulty, weight loss, 1 rat died later: autopsy (histol.) livers congested with necrosis and fibrosis

130 ppm (D, acetone): 2M 2F rats: 4 × 5-hr exposures: intense lachrymation, nose irritation, lethargy, weight loss: autopsy, organs normal

18 ppm (D, acetone): 2M 2F rats: 15 × 6-hr exposures: initial nose and eye irritation, lethargy, poor condition, retarded weight gain, blood and urine tests normal: autopsy, organs normal

6 ppm (D, acetone): 2M 2F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal

Sulphur chloride pentafluoride



vapour b.p. -20°C

100 ppm (F): 2M rats: 1 × 1-hr exposure: severe respiratory difficulty, both died: autopsy, lungs swollen and dark, (histol.) lungs—oedema and haemorrhage, liver and kidneys—congestion

20 ppm (F): 2M 2F rats: 1 × 5-hr exposure: respiratory difficulty: autopsy (histol.) lungs—oedema and congestion, liver and kidneys—congestion

5 ppm (F): 4M 4F rats: 3 × 5-hr exposures: respiratory difficulty, weight loss: autopsy (histol.) lungs—congestion and oedema

1 ppm (F): 4M 4F rats: 20 × 6-hr exposures: no toxic signs: autopsy, organs normal

pentafluorosulphur oxide



liq. b.p. 29°C

1000 ppm (D, cooled): 4F rats: 1 × 2-hr exposure: respiratory difficulty, narcosis, cyanosis, froth at nose, all died: autopsy, severe lung oedema

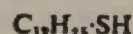
100 ppm (D, cooled): 4F rats: 1 × 2.5-hr exposure: respiratory difficulty, narcosis, cyanosis, all died: autopsy, severe lung oedema

20 ppm (D, pet. ether): 4F rats: 1 × 6-hr exposure: no toxic signs during exposure, 2 died later: autopsy (histol.) marked perivascular and peribronchiolar lung oedema, acute bronchitis

10 ppm (D, pet. ether): 4M 4F rats: 20 × 6-hr exposures: lethargy, respiratory difficulty, weight gain retarded: autopsy (histol.) lung oedema, liver, kidneys and spleen congested

5 ppm (D, pet. ether): 4M 4F rats: 20 × 6-hr exposures: no toxic signs: autopsy, organs normal

Lauryl mercaptan

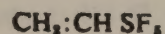


[dodecanethiol]

liq. b.p. 144-148°C (95 mm)

Saturated (A): 2M 2F rats: 20 × 6-hr exposures: no toxic signs: autopsy, organs normal

Vinylsulphur pentafluoride



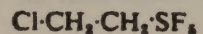
liq. b.p. 41°C

800 ppm (D, cooled): 2M 2F rats: 1 × 5-hr exposure: respiratory difficulty, lethargy, incoordination, 1 died: autopsy (histol.) livers—inflammation and fatty infiltration, kidneys—tubules dilated with degeneration

200 ppm (D, cooled): 2M 2F rats: 5 × 6-hr exposures: respiratory difficulty, lethargy weight loss, 1 died: autopsy (histol.) lungs—congestion and inflammation, livers—congestion and fatty infiltration, kidneys—tubules dilated with some degeneration

50 ppm (D, cooled): 4M 4F rats: 19 × 6-hr exposures: no toxic signs: autopsy, organs normal

2-Chloroethylsulphur pentafluoride

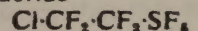


liq. b.p. 92°C

200 ppm (D): 4M rats: 1 × 2-hr exposure: tremors and convulsions, 1 died: autopsy, organs normal

50 ppm (D): 4M 4F rats: 20 × 6-hr exposures: no toxic signs: autopsy, organs normal

2-Chlorotetrafluoroethylsulphur pentafluoride



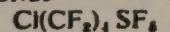
liq. b.p. 46.5°C

5000 ppm (D, cooled): 2M 2F rats: 1 × 3-hr exposure: respiratory difficulty leading to gasping and convulsions, all died during or soon after exposure: autopsy (histol.) lungs congested and oedematous, liver congested

1000 ppm (D, cooled): 2M 2F rats: 1 × 6-hr exposure: respiratory difficulty, 3 died after exposure: autopsy (histol.) lungs oedematous

200 ppm (D, cooled): 2M 2F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal

4-Chloro-octafluorobutyl sulphur pentafluoride



liq. b.p. 99°C

5000 ppm (D): 4M rats: 1 × 5-hr exposure: no toxic signs: autopsy, organs normal

500 ppm (D): 3F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal (slight lung congestion?)

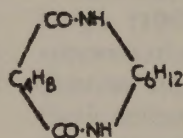
6-Chlorododecafluorohexylsulphur pentafluoride
liq. b.p. 143°C $\text{Cl(CF}_2)_6\text{SF}_5$
2500 ppm (D): 4F rats: 2 × 5-hr exposures: no weight gain: autopsy, organs normal
500 ppm (D): 4F rats: 13 × 6-hr exposures: no toxic signs: autopsy, organs normal

Miscellaneous

NN-Hexamethylenedipamide
solid, m.p. 250°C

Fume 18 mg/litre (H): 4M 4F rats: 15 × 6-hr exposures: no toxic signs: blood and urine tests normal: autopsy (histol.) liver cell vacuolation and necrosis

Fume 15 mg/litre (H): 4M 4F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal



Acrylyl chloride
[propenoyl chloride]
liq. b.p. 73°C

100 ppm (D): 4M rats: 1 × 2-hr exposure: lethargy, respiratory difficulty, autopsy, lung oedema

25 ppm (D, xylene): 4F rats: 1 × 4-hr exposure: eye irritation, respiratory difficulty, incoordination, 1 died: autopsy, lungs distended and oedematous, (histol.) lung emphysema and oedema

5 ppm (D, acetone): 4F rats: 5 × 5-hr exposures: eye irritation, respiratory difficulty, lethargy, low rectal temperature, weight loss, 3 rats died on 3rd day: autopsy (histol.) pneumonia

2.5 ppm (D, acetone): 4M 4F rats: 3 × 6-hr exposures: weight loss, low rectal temperature, 1 died: autopsy, lungs distended, (histol.) lung oedema and inflammation

1 ppm (D, acetone): 4M 4F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal

2,2-Bis-*p*-hydroxyphenylpropane $\text{Me}_2\text{C(C}_6\text{H}_4\text{-OH-}p)_2$
solid, m.p. 152-156°C
Saturated (B): 4M rats: 5 × 6-hr exposures: no toxic signs: autopsy, organs normal

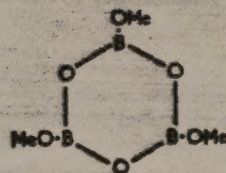
Ethyl 3-chlorophenylformimidate $3\text{-ClC}_6\text{H}_4\text{N:CH-OEt}$
liq. b.p. 120°C (15 mm)

Saturated (A) [0.26 mg/litre, 33 ppm]: 3M rats: 9 × 6-hr exposures: nose and eye irritation, lethargy, respiratory difficulty, weight loss: autopsy, lungs discoloured, (histol.) lungs—areas of consolidation and collapse with peribronchiolar lymphocytic reaction

22 ppm (D, ethanol): 6M rats: 11 × 6-hr exposures: slight lethargy and respiratory difficulty: autopsy, organs normal

Trimethoxyboroxine
liq. decomp.

Saturated (A) [3 mg/litre, 600 ppm]: 3 M4F rats: 9 × 6-hr exposures: slight lethargy: autops, organs normal



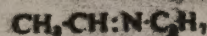
N-Propylethylideneamine
liq. b.p. 74°C

250 ppm (D): 4M 4F rats: 1 × 5-hr exposure: eye and nose irritation, respiratory difficulty (M more affected), poor condition: autopsy (histol.) increased macrophages in lungs

100 ppm (D): 4M 4F rats: 6 × 6-hr exposures: nose irritation, respiratory difficulty, lethargy, weight loss, 1 died, blood and urine tests normal: autopsy (histol.) increased macrophages in lungs

10 ppm (D, pet. ether): 4M 4F rats: 15 × 6-hr exposures: no toxic signs apart from retarded weight gain, blood and urine tests normal: autopsy, organs normal

5 ppm (D, pet. ether): 4M 4F rats: 15 × 6-hr exposures: no toxic signs: autopsy, organs normal

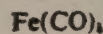


Iron pentacarbonyl
liq. b.p. 103°C

33 ppm (D, pet. ether): 4M 4F rats: 1 × 5.5-hr exposure: lethargy, respiratory difficulty, 4% carboxyhaemoglobin, 3 dead next day: autopsy (histol.) lung oedema and congestion

15 ppm (D, pet. ether): 4M 4F rats: 2 × 5.5-hr exposures: lethargy, respiratory difficulty, 0.2-0.4% carboxyhaemoglobin, 4 dead 3-4 days later: autopsy (histol.) lung oedema and congestion

7 ppm (D, pet. ether): 4M 4F rats: 18 × 5.5-hr exposures: no toxic signs: autopsy, organs normal



Discussion

Review of toxicological properties

Hydrocarbons None of the compounds examined showed any effects on the blood cells; the results with trimethylbenzene did not confirm the rather doubtful evidence that this compound has such an effect in man (Bättig, Grandjean, Rossi, and Rickenbacher, 1958). Soviet work (Korbakova, 1964) claims that low concentrations of cyclopentadiene and dicyclopentadiene can affect the blood as well as the lung and the functioning of the nervous system. Other Soviet work casts doubt on the low toxicity of isoprene, indicating marginal organ damage after prolonged exposure to 67-200 ppm (Korbakova and Fedorova, 1964).

Alcohols The alcohols examined show interesting features. *t*-Butoxyethanol had the characteristic haemolytic action of *n*-butoxyethanol described by Werner, Nawrocki, Mitchell, Miller, and von Oettingen (1943), and Carpenter, Smyth, and Pozzani (1949). The results strongly suggest that the alcohol

or its metabolite (Carpenter, Pozzani, Weil, Nair, Keck, and Smyth, 1956) increases the fragility of aged red cells, and that the effect disappears when the average age is reduced by haemopoiesis, returning only when the normal age distribution is restored. Isopropoxyethanol shows the same effect but to a lesser extent. Perfluoro-triethylcarbinol is a powerful uncoupler of oxidative phosphorylation, an effect which has been confirmed by *in vitro* studies on mitochondria in which a dissociation between oxygen uptake and the phosphorylation of ADP was observed which was quantitatively and qualitatively similar to that from dinitrophenol (Gage, unpublished work). This compound must be one of the simplest to show this effect; it conforms to the requirements of an uncoupler (Hemker, 1962) in that it is acidic due to the influence of the fluorine atoms on the hydroxyl group, and it is lipid-soluble in its non-ionized form. Chloropropanol is irritant but it does not show the central effects of chloroethanol (Goldblatt and Chiesman, 1944).

Ethers All the ethers had the central depressant action of diethyl ether, with the exception of dichlorodiisopropyl ether, which showed irritant properties, like its ethyl homologue (American Petroleum Institute, 1948).

Aldehydes and ketones The aldehydes have anaesthetic properties, with no marked irritant action. According to Skog (1950), the LC_{50} (30 minutes) of butyraldehyde to rats is 6% v/v. Sim and Pattle (1957) state that groups of men exposed to concentrations of butyraldehyde and isobutyraldehyde greater than 200 ppm for 30 minutes experienced no irritation, but some nausea with isobutyraldehyde. Soviet investigations on man (Uloyan, 1965) claim that a variety of effects are produced at 3 ppm.

Acids A comparison of the results with acrylic and methacrylic acids demonstrates the reduction in irritant action by the introduction of a methyl group, an effect observed with the methyl esters which show a 10-fold difference in American Conference of Governmental Industrial Hygienists (ACGIH, 1968) threshold limit values. The low toxicity of methacrylic acid in animals is in conflict with Soviet claims (Stulova, Rummyantseva, and Ivanova, 1962) that concentrations down to 6 ppm produce marginal changes in the function of the nervous system in man.

Chlorinated hydrocarbons The aliphatic chlorinated hydrocarbons demonstrated the liver and kidney damage characteristic of some members of this series. The two unsaturated 4-carbon compounds, dichlorobutene and hexachlorobutadiene, are highly toxic; both are capable of producing severe kidney

damage, but with dichlorobutene lung irritation predominates and the renal effect has been observed only after percutaneous absorption (Ferguson, unpublished work). Smyth, Carpenter, and Weil (1951) found that exposure of rats for 4 hours to 62 ppm dichlorobutene (isomer unspecified) killed 2/6. The chlorinated ethylenes, on the other hand, are of relatively low toxicity. The results with 1,1-dichloroethene are extended by the observations of Prendergast, Jones, Jenkins, and Siegel (1967), who found no clear toxic manifestations apart from a retarded weight increase in a variety of species exposed to 100 ppm 5 hours/day for six weeks, while some liver damage was found after continuous exposures 24 hours/day to 47 ppm for 90 days. Rylova (1953) states that 25 ppm is irritant to man.

Pentafluorobenzene is a narcotic; Garmer and Leigh (1967) have shown that the anaesthetic concentration for cats is 1.5-2.5% v/v. As the fluorine atoms are replaced by chlorine, the anaesthetic action remains but a cytotoxic action appears, together with an effect on porphyrin metabolism.

The results with chloronaphthalene are in contradiction to Soviet claims (Kapkaev, 1957) that concentrations in the region of 1 ppm cause liver damage with a variety of blood changes and a hyperacidic gastritis.

Esters The unsaturated esters of saturated carboxylic acids are typically of low toxicity, high concentrations producing irritation and narcosis. With the exception of vinyl acetate, none of the esters of this type which have been examined was sufficiently volatile to show these effects. Dimethyl carbonate rapidly hydrolyses so its toxicity may be taken to be that of methanol. The high toxicity of the chloroformates is due to their great chemical reactivity; presumably like phosgene they modify cell membranes to produce permeability changes. Methyl nitrite produced methaemoglobinaemia *in vivo* at a rate similar to that of sodium nitrite; if its action is due to inorganic nitrite then its hydrolysis *in vivo* must be very rapid.

Amines The amines examined showed irritant and central stimulant effects; these increased with the degree of substitution, but the higher members have too low a volatility to present a significant vapour hazard. The results with diaminoethane are in contradiction to Soviet claims (Kulakov, 1967) that changes in the blood cells and in motor responses are seen in rats at 0.04 mg/m³.

Nitriles The compounds tested were primarily irritant, and there is no clear indication that any of the effects observed were due to liberated cyanide.

Heterocyclics There are no notable common features in this group.

Organic peroxides These compounds were irritant to the eyes and respiratory tract, presumably because of their high reactivity, but it is not possible to relate their toxicity to their reactivity with iodide solution. The results obtained with cumene hydroperoxide may be compared with those of Floyd and Stokinger (1958), who found the LC_{50} (4 hours) to be 220 ppm in rats. Soviet claims (Solomin, 1964, 1966) suggest that the concentration of this compound must be reduced to 0.001 ppm to avoid effects on animals and on man.

Organic phosphorus compounds Trishydroxymethylpropane phosphite has shown an unexpectedly high toxicity; it is one of the most toxic compounds handled in this laboratory. It is fairly readily hydrolysed to yield dihydroxybutylphosphonic acid, which is of low toxicity by oral or parenteral administration. Its marked action on the central nervous system is probably due to its having sufficient stability to penetrate cell membranes as a non-ionized molecule, and its ultimate action may be due to its hydrolysis product or a reaction *in situ*.

Diethyl phosphorochloridothionate is primarily an irritant, presumably due to the reactive chlorine atom, but it is also a weak *in vivo* inhibitor of cholinesterase.

Silicon compounds The toxicity of silicon tetrafluoride is probably due to hydrogen fluoride released by hydrolysis. Similarly, the irritant action of silicon tetrakisocyanate may be due to isocyanic acid. The stable silane derivatives are of low toxicity.

Sulphur compounds This group contains members which, presumably because of their high reactivity, are powerful lung irritants. Sulphur chloride pentafluoride, bispentafluorosulphur monoxide, and trichloro-methylsulphenyl chloride are at least as toxic as phosgene. The toxicity of sulphur dichloride is probably due to hydrolysis to hydrogen chloride. Vinylsulphur pentafluoride and divinyl disulphide have, in addition to their irritant action, a toxic effect on the liver or kidneys.

Miscellaneous Iron pentacarbonyl is a lung irritant, it affects the central nervous system and causes liver and kidney damage. A measurement of blood carboxyhaemoglobin would provide no guide to intoxication.

The value of inhalation experiments

Most of the substances which have been tested in these inhalation experiments have also been studied in these laboratories for oral and parenteral toxicity and for their effects on the skin and eyes. The systemic effects elicited after oral or intraperitoneal administration, or by percutaneous absorption,

give, in general, a qualitative indication of the systemic effects obtained by inhalation studies, but, because of the differences in rates of absorption and metabolic transformations, there is little useful quantitative information.

Inhalation experiments are of special value for the study of those compounds which have an immediate or delayed irritant action on the lungs, for the intensity of these effects cannot be predicted with any certainty by other routes of administration. A survey of the results gives a strong indication that these effects on the lung are associated with the chemical reactivity of the molecule, particularly if the onset of severe symptoms is delayed. It seems probable that there is an initial modification of cell membranes, as postulated for the action of phosgene and ketene, followed by permeability changes leading to oedema and haemorrhage.

After short exposures to high concentrations of lung irritants, the effects seen at histological examination of lung tissue indicate that death can be attributed to an interference with gas exchange. After more prolonged exposure to lower concentrations, the cause of death is less certain, for although lung changes may be apparent, they are sometimes insufficient to account for the lethal action. Moreover, at still lower concentrations the animals may be in poor condition with a diminished weight increase, without any trace of damage being detectable in the lungs. It seems likely that exposure to irritant gases and vapours gives rise to stress which is responsible for the marginal toxic effects, and it is possible that the occasional observation of a diminution in the size of the thymus may be in some way connected with such stress effects.

Provisional operational limits

Subacute inhalation experiments lasting approximately three weeks cannot be regarded as an adequate basis for the establishment of threshold limit values which will define safe working concentrations under all conditions, although a study of the origins of the list published by the ACGIH (1966) shows that some of their values have been derived from more tenuous evidence. Nevertheless, the results obtained in these investigations permit an assessment of the toxic hazard which is of value to the chemical engineer in the design of plant, or which can form the basis of a code of safety precautions provided that those exposed are under adequate medical supervision. The limiting concentration derived from these experiments may be termed provisional operational limits to distinguish them from threshold limit values, which should preferably be based on more extended experiments on a variety of species, supported by evidence from human exposure.

The limits in Table 1 have been derived from the

TABLE 1 (continued)

Trichloromethylsulphenyl chloride ..	0.1
Sulphur chloride pentafluoride ..	0.5
Bispentafluorosulphur oxide ..	0.5
Dimethyl disulphide	5
Divinyl disulphide	2
Vinyl sulphur pentafluoride	20
2-Chloroethyl sulphur pentafluoride	20
2-Chlorotetrafluoroethyl sulphur	
pentafluoride	20
4-Chlorooctafluorobutyl sulphur	
pentafluoride	100
6-Chlorodecafluorohexyl sulphur	
pentafluoride	250
Acrylyl chloride	0.1
Ethyl 3-chlorophenylformimidate ..	5
Ethylidene propylimine	2
Iron pentacarbonyl	2

TABLE 2

SOVIET RECOMMENDED MAXIMAL ALLOWABLE
CONCENTRATIONS

	ppm	
Isoprene	17	Korbakova and Fedorova (1964)
Cyclopentadiene	2	Uloyan (1965)
Methacrylic acid	0.003	Stulova, Rummyantseva, and Ivanova (1962)
Butyraldehyde	0.3	Korbakova (1964)
Diaminohexane	0.0002	Kulakov (1967)
Cumene		
hydroperoxide	0.001	Solomin (1966)

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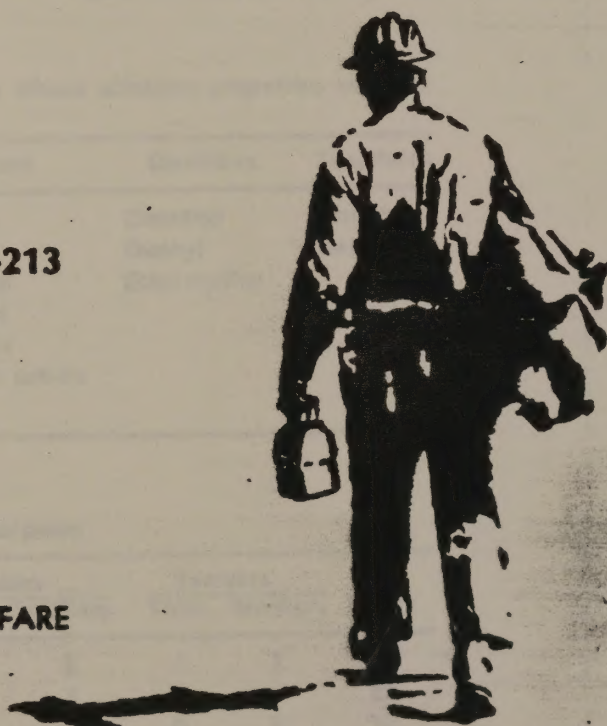
CRITERIA FOR A
RECOMMENDED STANDARD....

OCCUPATIONAL
EXPOSURE TO

- **n-ALKANE MONO THIOLS**
- **CYCLOHEXANETHIOL**
- **BENZENETHIOL**

DHEW (NIOSH) Publication No. 78-213

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health



Variation in Recognition Odor Threshold of a Panel

Frank V. Wilby

California Gas Company

to correlate the odor strength of natural gas with its sulfur analysis, the recognition odor thresholds of 18 sulfur compounds were determined using an untrained panel of 35 people. For each test a series of odor concentrations graduated in increments of $10^{0.2}$ was presented to the panel in random order over a range of concentrations above and below the olfactory thresholds of all panelists. Each odor was tested on at least three different days. Desired odor concentrations were produced by dynamic blending of gaseous mixtures of the odorous compounds with air. All testing was done out-of-doors during clement weather when no ambient odors were apparent. The range of olfactory response was found to be much greater for certain compounds than for others. Branching of the hydro-carbon chain increased odor strength. Certain compounds appeared to evoke anomalous responses.

Certain compounds appeared to evoke anomalous responses.

Sulfur Compounds Investigated

The Pacific Lighting System presents one of the more complex odor problems to be found in a gas utility because of its multiplicity of gas sources whose quantitative and qualitative sulfur composition vary continually. Over 35 naturally occurring organic sulfur compounds have been found in our natural gas.¹ The more predominantly occurring sulfur compounds listed in Table I were selected for study.

The di- and trisulfides were included since they may occur in significant olfactory concentrations; being formed by the oxidation reactions of mercaptans and hydrogen sulfide.

Odor Panel Composition

Since the study was directed toward understanding the olfactory response of gas customers who are likely to be concerned with gas odor, only persons over 18 years old were included in the panel. The members were chosen so as to approximate the age and sex distribution of the U. S. adult population. Smoking was not a basis for selection, although the data for smokers were examined for significant effects. All panelists were office employees of the Southern California Gas Co., working in one building and having jobs which permitted their regular participation in a series of odor tests conducted over a period of almost

five months.

panel is shown.

Except for one who was completed testing experience in relation to gas odor, the objective was to select at least thirty people in a series covering five months, seven were included in the expected turnover. Ten panelists, more than 75% of the total, are listed in this report.

Panelists were selected on the basis of age, sex, and the use of odor. After admonition to refrain from chewing gum, or using perfume, and the use of odor, the younger women were included on the standpoint of dereliction had been determining the people under the conditions.

The total panel was divided into four groups, since the maximum number of tests tested converted were made on the panel. One half the panel was tested in the morning and the other half in the afternoon. This was done to eliminate effects. Each minimum of three tests was given to each person tested on four

Method of Odor

The recognition threshold was determined under the odor condition when no other odors were apparent. The temperature was 80° F, rain, etc. on the roof of the

Table I. Sulfur compounds whose olfactory properties were investigated

Mercaptans	Sulfides	Disulfides	Trisulfides
Methyl	Dimethyl	Dimethyl	Dimethyl
Ethyl	Diethyl	Diethyl	Diethyl
n-propyl	di-n-propyl	Ethyl methyl	
i-propyl	di-i-propyl		
n-butyl	Thiophane		
i-butyl	Hydrogen sulfide		
t-butyl			

Table II. Composition of odor panel

Age Groups	Males		Females		Totals
	Total	Smokers	Total	Smokers	
18 - 35	5	2	4	1	9
36 - 55	6	4	7	4	13
56 - 66	7	4	6	2	13
Totals	18	10	17	7	35

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Table III. Frequency of wrong response to zero odor level

Numbers of Observers	Wrong Response to Zero Odor Level	
	Number	Per Cent
7	0	20
8	1	23
6	2	17
6	3	17
8	Over 3	23
Totals 35		100

five months. The composition of the panel is shown in Table II.

Except for two members, the panel was completely without previous odor testing experience and had had no relation to gas odorization. Since the objective was to maintain a panel of at least thirty people during the entire test series covering a period of almost five months, several alternate members were included to provide for the expedient turnover. The test results of ten panelists who participated in less than 75% of the tests are not included in this report.

Panelists were required not to smoke, chew gum, or eat candy during the test period and they were cautioned against the use of odorous cosmetics. This latter admonition proved impossible to enforce in the case of several of the younger women. From the practical standpoint of the gas industry, this selection had the mitigating effect of determining the odor thresholds of these people under their normal olfactory conditions.

The total panel was divided into two groups, since 15 to 18 people was about the maximum number that could be tested conveniently at one time. Tests were made on Tuesdays and Thursdays. One half the panel reported Tuesday morning and Thursday afternoon, and the other half at the opposite times. This was done to minimize time of day effects. Each odor was tested on a minimum of three different days. During a given test period, the panel was tested on four different odors.

Method of Olfactory Testing

The recognition odor thresholds were determined under "normal" ambient conditions, i.e., Los Angeles air with no obviously interfering factors were apparent such as smog, fog, wind, etc., temperatures below 60 or above 80°F, rain, etc. All tests were conducted on the roof of a 13-story building in

downtown Los Angeles. The air at this elevation is relatively clean and we were favored with winter and spring weather having unusually clean air. Four compounds were tested during a given session. Each compound was tested on three different days.

The test scheme was devised to yield the most information in the least amount of time and to be as simple and objective as possible for the use of untrained panel members. The scale of concentrations was based on the fifth root of ten ($10^{0.2}$) i.e., a geometric progression having increments of about 59%. This increment was chosen because previous experience had indicated it is about the lowest most observers can discriminate reliably. Also, it was estimated the experimental errors in preparing the diluted gas mixture would be significantly less than this amount. A hundredfold concentration range and a setting of zero was covered by 12 concentration settings. For a few compounds it proved that a somewhat greater concentration range was needed to include all observers at all times.

The order of presentation of the 12 concentrations was random, being determined by lot. A concentration of zero was included as a check on guessing by the panelists. Three dynamic gas blenders or odorometers were operated simultaneously from the same tank of odorized gas. At the start of a test, all panelists were allowed a smell of the odor at a concentration sufficiently high to be detectable to all. This was so the panelists would be able to recognize the odor being tested.

For the odor test the panelists walked in single file past the three odorometers, pausing at each to take one or two breaths. They then checked the appropriate square on their test card whether they detected the odor or not. If there was any doubt, they were to report the odor as not detected. Even as simple a test format as this is subject

to inadvertent errors, mainly from transposition of the checks on the report form. In evaluating the observer's report form for each test, his threshold concentration was taken as the lowest concentration he could smell consistently, not just the lowest one he reported.

In each test a concentration of zero was always included as a check on guessing and transposition of check marks into the wrong column on the observer's test card. The number of times the zero concentration was wrongly recorded by each observer during the series of approximately 100 tests is shown in Table III.

Preparation of Odor Samples

To obtain the necessary quantitative dilution of the sulfur compounds to their olfactory threshold concentrations in the parts per billion range, a two-step dilution procedure was employed. The first step was to prepare a gas mixture of highly purified methane containing a few parts per million of the desired sulfur compound. This gas mixture was contained at 200 psig in specially constructed 1.7 cf stainless steel pressure vessels.

To desorb any compounds previously contained the tanks were first heated to about 300°F and alternately purged with pure methane and evacuated. After cleaning, the approximate amount of sulfur compound was added to the tank. The tank was then pressured to 200 psig with purified methane and allowed to equilibrate for at least 24 hours. A quantitative sulfur analysis was then made using the methylene blue method for hydrogen sulfide² and hydrogenation with methylene blue finish¹ for other sulfur compounds. These analyses were run each time the tank was used, usually at least three times. When mercaptans were tested, a gas chromatographic analysis¹ was also made to determine if there had been

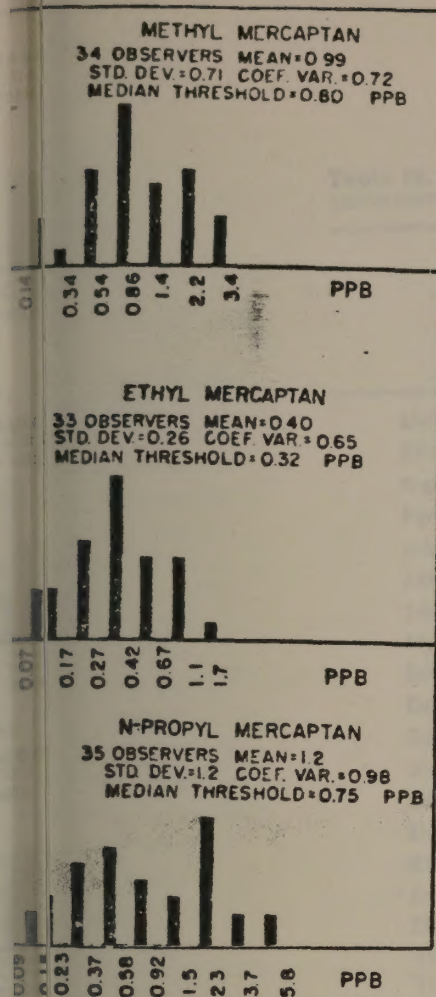


Figure 1.

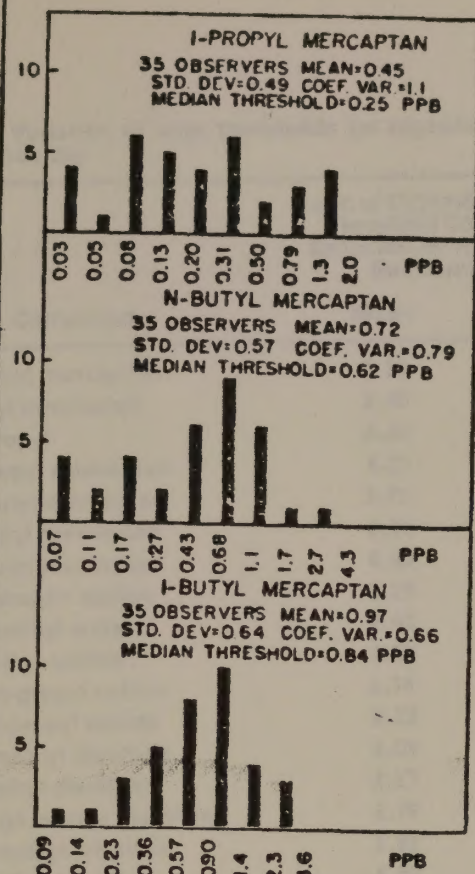


Figure 2.

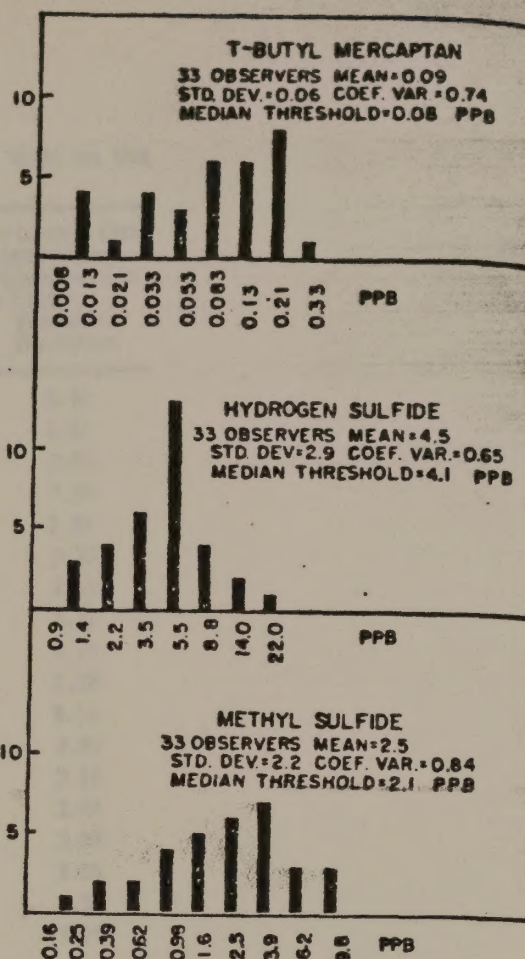


Figure 3.

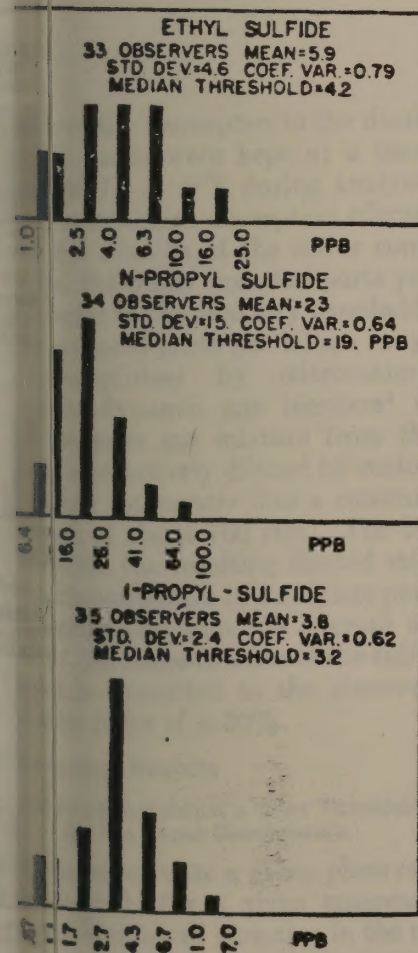


Figure 4.

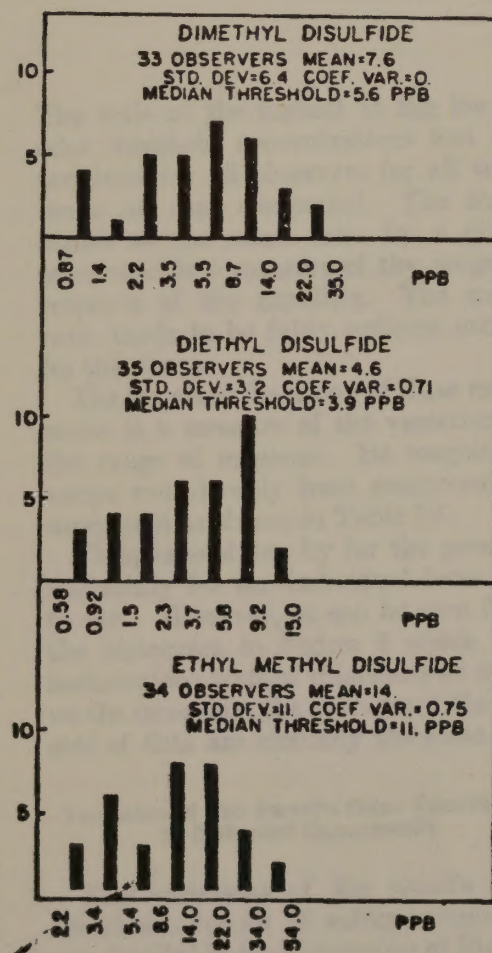


Figure 5.

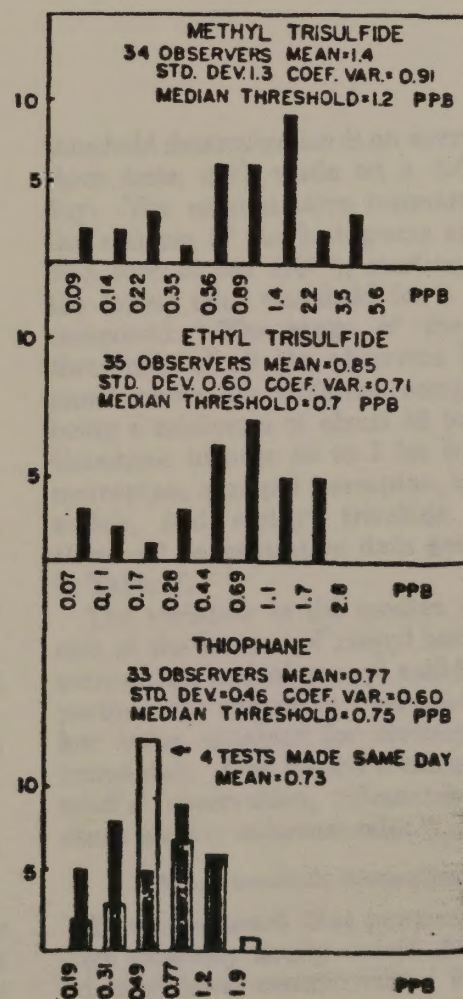


Figure 6.

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Table IV. Variation of odor thresholds for repeated tests on the same compounds

Compound	Ratio of Highest to Lowest Odor Threshold Concentrations Detected by All Observers in Successive Tests ^a	
	Mean	Standard Deviation
Methyl mercaptan	3.15	3.02
Ethyl mercaptan	2.80	1.62
n-propyl	3.20	2.85
i-propyl mercaptan	4.23	7.20
n-butyl mercaptan	3.25	2.24
i-butyl mercaptan	3.51	2.77
t-butyl mercaptan	4.30	4.15
Hydrogen sulfide	3.29	1.71
Dimethyl sulfide	2.69	1.71
Diethyl sulfide	2.92	2.28
Di-n-propyl sulfide	3.74	3.55
di-i-propyl sulfide	3.23	2.99
Dimethyl disulfide	3.09	2.10
Diethyl disulfide	3.17	2.47
Ethyl methyl disulfide	3.79	3.87
Dimethyl trisulfide	3.99	3.04
Diethyl trisulfide	4.89	4.50
Thiophane	8.78	9.29
Thiophane (4 tests same day)	2.97	1.82
Mean	3.72	3.32

^a All compounds except the last thiophane test were tested on three different days.

of the mercaptan to the disulfide tanks were kept at a temperature of $75 \pm 5^\circ\text{F}$ during analysis to minimize absorption effects. The final dilution of the sulfur compounds in the tanks from the parts per million range to the olfactory thresholds in the fractional parts per billion range was accomplished by odorometers. These are dynamic gas blenders⁴ in which the ppm gas mixture from the tank is quantitatively diluted by metered air through rotameters into a constant stream of about 100 cfm. The observer smells the resulting diluted mixture through a 10-in. square port. It is estimated that the over-all accuracy of the concentration of the sulfur compounds presented to the observers is of the order of $\pm 30\%$.

Experimental Results

Variation of Individual's Odor Thresholds for the Same Compounds

In successive tests a given observer's threshold for a given compound varies because of variation in the olfactory physical and mental response and changes in ambient conditions.

The ratio of the highest to the lowest odor threshold concentrations was determined for all observers for all tests made on each compound. The magnitude of the mean ratio for a given compound is a measure of the range of response of the panelists. The mean ratio tends to be fairly uniform except for thiophane.

The standard deviation of these mean ratios is a measure of the variation in the range of response. Its magnitude varies considerably from compound to compound as shown in Table IV.

Thiophane shows by far the greatest variability for the individual from test to test. However, as can be seen from the histogram in Figure 6 which also includes four tests of thiophane all made on the same day, the averages of the two sets of data are virtually the same.

Variation of the Panel's Odor Thresholds to Different Compounds

The variations of the panel's odor thresholds for all 18 sulfur compounds are detailed in the histograms of Figures 1 through 6. For each observer each

threshold determination is an average of three tests, each made on a different day. The concentration increments of the abscissa of the histograms are the fifth root of ten ($10^{0.2}$), starting from the lowest odor threshold for a given compound. The range of the odor thresholds of all the observers in the panel varies for different compounds being a minimum of about 10 to 1 for thiophane to over 50 to 1 for i-propyl mercaptan, n-propyl mercaptan, methyl sulfide, and methyl trisulfide. The threshold concentration data are given in Table V.

The variation in the median thresholds of the isomers of propyl and butyl mercaptans and of propyl sulfide were particularly surprising; especially the low value obtained for tertiary butyl mercaptan. Our results confirm Moncrieff's⁵ observation, "Branching of a chain usually enhances odor."

Odor Threshold Anomalies

It was assumed that persons having high olfactory acuity would detect all odors at lower concentrations than the average person and conversely for those

Table V. Odor threshold concentrations of sulfur compounds

Compound	Median, ppb ^a	Mean, ppb ^a	Standard Deviation	Coefficient of Variation
ethyl mercaptan	0.80	0.99	0.71	0.72
propyl mercaptan	0.32	0.40	0.26	0.65
isopropyl mercaptan	0.75	0.75	1.2	0.98
butyl mercaptan	0.25	0.45	0.49	1.1
tert-butyl mercaptan	0.62	0.72	0.57	0.79
isobutyl mercaptan	0.83	0.97	0.64	0.66
sec-butyl mercaptan	0.08	0.09	0.06	0.74
hydrogen sulfide	4.1	4.5	2.9	0.65
dimethyl sulfide	2.0	2.5	2.2	0.84
diethyl sulfide	4.2	5.9	4.6	0.79
n-propyl sulfide	19.	23.	15.	0.64
i-propyl sulfide	3.2	3.8	2.4	0.62
dimethyl disulfide	5.6	7.6	6.4	0.83
diethyl disulfide	3.9	4.6	3.2	0.71
ethyl methyl disulfide	11.	14.	11.	0.75
trimethyl trisulfide	1.2	1.4	1.3	0.91
diethyl trisulfide	0.7	0.85	0.60	0.71
thiophane	0.75	0.77	0.46	0.60
Mean = 0.76				

^aAll concentrations on a volume basis.

poor sense of smell. An attempt to determine if this is true, and if so, to use this for detecting anomalous olfactory responses. The following procedure:

For each compound the panelist's odor thresholds were arranged in ascending order and the difference between the lowest and highest odor thresholds was divided into ten equal logarithmic increments, i.e., "log deciles." The people whose odor threshold fell in the first log decile were ranked one, the second, up to ten for the tenth decile. Thus, the odor threshold of each person was placed on a scale of one to ten for each compound relative to all members of the panel.

Analysis of these data showed that the observer tended to maintain a consistent sensitivity ranking from compound to compound.

For each compound the deviation of the log decile ranking from the average ranking for all 18 compounds was calculated. The magnitude of this latter number is a

measure of how far a person deviates from his average olfactory threshold rank relative to the other members of the panel. A large deviation is an indication of anomalous olfactory response.

It was noted that for those compounds, such as *di-n*-propyl sulfide, thiophane, and *t*-butyl mercaptan, showing the greatest number of anomalies, the large deviations all tended to be in the same direction for a given compound. This indicates that for those compounds exhibiting pronounced anomalous olfactory responses a considerable number of people tend to be either significantly more or significantly less sensitive to that particular compound.

Tertiary butyl mercaptan appears to show the most anomalous behavior. Although its median odor threshold is by far the lowest of the compounds tested, the large deviations are mostly positive, i.e., the odor threshold for those people is much higher than would be expected. Enough tests were made in this study to indicate that anomalies do exist, but to accurately quantify them would require much more data.

Summary

The recognition odor thresholds of 17 organic sulfur compounds and hydrogen sulfide were determined using an untrained panel of 35 men and women. The compounds tested are those likely to be found as olfactory warning agents in natural gas. Although most people seem to be fairly consistent in their olfactory acuity, some compounds evoke anomalous responses. This results in either a greater or less than expected response of a significant number of people to certain compounds. This work confirmed that branching of a chain usually enhances odor.

Acknowledgments

This work was sponsored by J. L. Oberseider of Pacific Lighting Service and Supply Co. H. M. Curtis supervised the odor tests and data processing.

References

1. Wilby, F. V., "Determination of sulfur compounds in natural gas by gas liquid chromatograph using low temperature sample concentration, temperature programming and microcoulometric titration," *Am. Gas Assoc., Operating Sect. Proc.*, Paper 65-P-136 (1965).
2. Mason, D. McA., "Investigation of standard methods of analysis for sulfur in natural gas," *Inst. of Gas Tech., Project PB-47, Final Report, Appendix I*, *Am. Gas Assoc.* (June 1963).
3. *Ibid*, Appendix II.
4. Wilby, F. V., "The odor comparator, an improved instrument for quantitative odor measurement," *Am. Gas Assoc. Production Conf.*, Paper 64-P-225 (1964).
5. Moncrieff, R. W., "The chemical senses," 2nd Ed., Leonard Hill, Ltd., London (1951).

The Air Pre

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Speed Letter.

John Teske

From

Dennis Meyers
Bio-Serv Inc.

I am enclosing the technical bulletin for
methyl di sulfide. Safety and handling information
included.

Date

6/18/82

Signed

Dennis Meyers

Date

Signed

A-23

RETAIN WHITE COPY, RETURN PINK COPY

Dimethyl Disulphide SNPA is presented as a pure organic liquid product which provides a source of sulphur in usable and practical form. It is a yellow liquid only slightly toxic and slightly inflammable. It decomposes at 150 °C into methyl mercaptan and hydrogen sulphide. As with most sulphur compounds it has a characteristic odour.

As a source of pure sulphur it is extremely useful in Petrochemical production, for example :

- In ethane cracking as an anti-corrosion and anti-coking additive
- In sulphiding of hydrogenation catalysts
- In de-alkylation reactions of aromatic nuclei as inhibitor of hydrocracking reactions.

And in General Chemical Reactions D.M.D.S. is extremely useful as a solvent and intermediate in synthesis of many sulphur-bearing compounds.

PHYSICAL PROPERTIES OF DIMETHYL DISULFIDE OR 2,3 DITHIA-BUTANE

IDENTIFICATIONS

SNPA	68	Method SNPA
Expressed in sulphur below ± 0,05 %		Method SNPA
	< 0,1 %	Method SNPA
Initial boiling point	108 °C	ASTM
95 %	110 °C	D 8,654
204	1,062 à 1,065	AFNOR NFT 60.101
	< 1 Echelle GARDNER	
	< 100 Echelle APHA	
	above 99 %	(chromatographic determination)

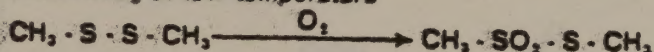
Properties are as follows :

Content (weight per cent)		88,1 %
Boiling point		- 84,72 °C
Boiling point (°C under 760 mm Hg)		109,60 °C
Density (g/ml)	20 °C	1,0625
	25 °C	1,0569
	30 °C	1,0514
Pressure (mm Hg)	25 °C	28,6
	55 °C	115,0
	103 °C	633,0
	128 °C	1268,0
Viscosity (cp)	20 °C	0,619
	25 °C	0,585
	30 °C	0,555
Surface tension (dynes/cm)	20 °C	33,6
	25 °C	32,8
	30 °C	32,2
Refractive index	Helium T	20 °C 1,52103
	V	20 °C 1,53473
	Hydrogène C	20 °C 1,52163
	F	20 °C 1,53683
	Sodium D	20 °C 1,52592
	Mercur E	20 °C 1,52970
	G	20 °C 1,54577
Heat constant °C-1		0,030
Heat of vaporisation cal/mole		9.181 ± 75
Heat capacity Cp cal deg. k¹/mole à 25 °C		22,54
Heat of formation cal deg. k¹/mole à 25 °C		80,46
Heat of formation kcal/mole à 25 °C		- 36,59
Heat of formation kcal/mole à 25 °C		16
Heat of formation kcal/mole		- 15,6

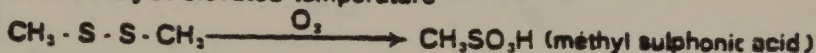
CHEMICAL PROPERTIES

Oxydation

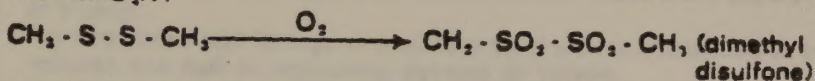
With HNO₃ at low temperature



With HNO₃ at elevated temperature

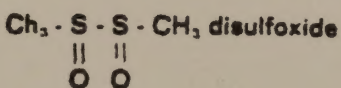
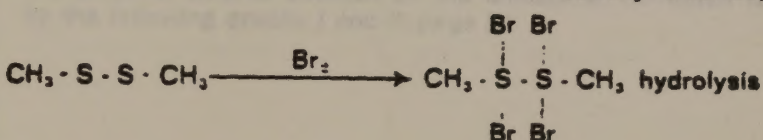
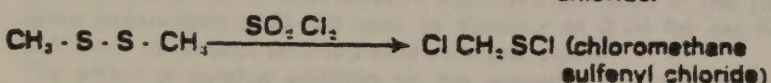
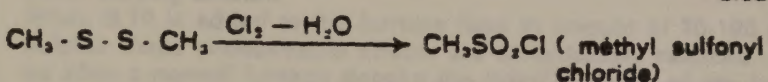
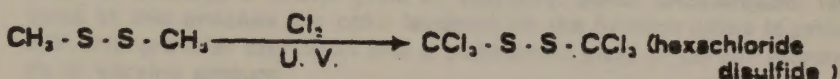
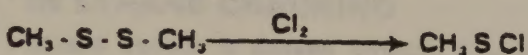


With MnO₂/K :



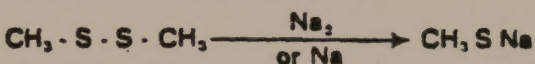
Methyl sulphonic acid can be prepared with electrolytic oxydation.

Action of halogens

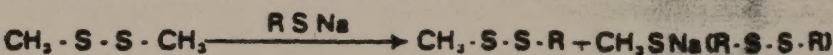


Réduction

Disulfides can give mercaptans :

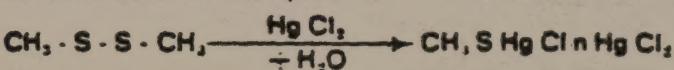


Dismutation reaction can be observed :



Complexing

Several metallic salts can be complexed with dimethyldisulfide with mercuric salts for example :



SULPHIDING OF HYDROGENATION

LISTS

In the early period in the life of a new catalyst high activity can be maintained which shortens the eventual life of the catalyst. If S 70 is used with the catalyst the reaction is controlled at all stages and a steady state is reached. It is thought that sulphur protects the catalyst in the early period that light coke deposits do when the catalyst has been in use for some hours.

Operation with S 70 present is complex. The catalyst performs at slightly lower temperatures. Thus the pressure of the reaction may be raised without affecting the partial pressure of hydrogen. The ratio of hydrogen to hydrocarbon is slightly improved. The reactors permit the run continuing to a higher end point than without S 70 and a substantially longer life. The amount of S 70 is adjusted according to the catalyst poisons or promoters present in the feed.

Operation as follows:

S 70 in Steam Cracker Gasoline Hydrotreating

Used to inhibit side reactions and block the olefin hydrogenation. First Step Reaction. Only gums which consist of di-olefins are removed and the product gasoline made suitable for motor fuel.

S 70 in Second Step Hydrogenation Reaction

Steam cracked gasoline is hydrogenated to convert olefins to paraffins in preparation for extraction of aromatics benzene toluene etc. 100 kilograms of sulphur per ton of catalyst are recommended for a pretreatment.

MoS₂ + H₂ + 2H₂S → MoS₂ + 3H₂O

$$\Delta H = -39 \text{ kilo cal/mole}$$



$$\Delta H = -31 \text{ kilo cal/mole}$$

When a concentration of S 70 is used it is possible to form Ni₃S₂. NiS will tend to revert to Ni₃S₂ as the concentration re-

HYDROALKYLATION REACTION

When S 70 is in pretreatment of the catalyst at 400 °C and 150 psi hydrogen pressure before commencing feed, and also during the run 15-20 ppm are continuously injected. At shut-down the hydrogen feed is discontinued and S 70 continued until hydrogenation of the hydrocarbons is complete.

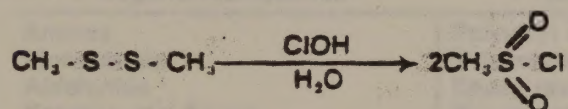
Methyl groups on the benzene nucleus are hydrogenated to methyl groups. With S 70 present and recycle aromatics 96-98 % yields are obtained.

Important in this reaction is the plant steelwork. A small quantity of 13 milligrams per cubic metre of Hydrogen should be sufficient to passivate the reactor steelwork.

STORAGE LINES AND FITTINGS

It is recommended to cover the ground of installations using S 70 with a cement floor and barrier to prevent spillage into the soil.

A solution of hypochlorite is recommended for destroying the spillage drips of D.M.D.S. The reaction is exothermic and care should be taken if the spillage is large.



Storage tanks may be of mild steel and it is not necessary to use special steels or coatings. It is recommended to use a dry blanket gas at 5 psig.

Transfer lines and fittings in stainless steel are recommended to avoid leakage and rust in measuring devices or valves.

An example of a feed installation is shown in page IV.

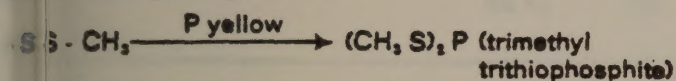
IN ETHANE CRACKING

Ethane vapour is passed through a furnace at high temperature in order to produce a further yield of ethylene. Some undesirable features of this process are coke laydown on the furnace tubes together with intergranular corrosion and a substantial yield of carbon monoxide in varying amount.

When S 70 is added to the furnace feed in amount of 70-100 ppm as sulphur these undesirable effects are considerably reduced. At start up after a normal furnace decoke the metal surfaces of the tubes require passivation: 400-500 ppm as Sulphur of S 70 for six hours is sufficient to control unfavourable catalytic action.

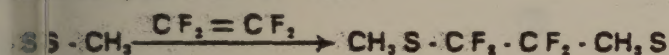
The effect of sulphur addition on the amount of corrosion is shown by the following graphs I and II. page IV.

Reaction with phosphorus

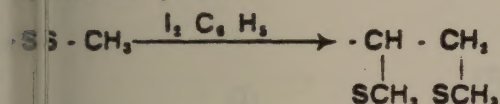


Reaction with olefinic compounds

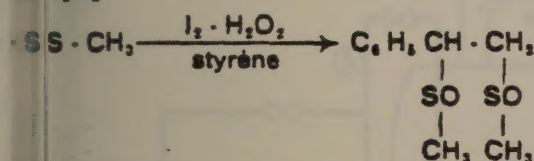
additive compound can be made:



styrene (and I_2 trace):



with H_2O_2 :



TOXICITY

D.M.D.S. is a liquid which is highly malodorous but very slightly toxic. Personnel will immediately detect the odour and are unlikely to be exposed to a high concentration.

Reaction with the skin should be avoided using gloves and clothing held under air supply. An air mask is also necessary in high concentrations of vapour.

Reaction with the eyes or skin

If the eyes or skin are contacted with D.M.D.S. the operator should wash the eyes or skin with copious quantities of pure water. If the irritation persists a doctor should be consulted.

First Aid

Move to fresh air.

First Aid

In case of a large ingestion the patient should be made to vomit by fingers in the throat or a glass of warm salt water.

STATIC ELECTRICITY

Installations must be equipped with a system which ensures the discharging to earth of all static charges.

DISTRIBUTION

Capacity: 225 Litres

Containers

on Road Tankers

on all Cars.

D.M.D.S. IN GENERAL CHEMICAL REACTIONS

D.M.D.S. AS A SOLVENT

The solvent action of D.M.D.S. has been examined in research. Extractions are able to be at 99 % and examples are given below. D.M.D.S. dissolves in the cold:

Organic Compounds	Organic Polymers
Amines Mono acids Aldehydes Ketones and Esters Ethers Hydrocarbons Halogens Alcohols Many phenols	Polyvinyl Pyrrolidone Butylmethacrylate Epoxy resins Polystyrenes

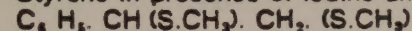
D.M.D.S. dissolves in the warm:

Organic Compounds	Organic Polymers
Amines Polyalcohols Acid anhydrides Many poly phenols	PVC PV Butyral Butadiene Styrene 40/60 GRS rubbers Formaldehyde ureas

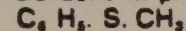
D.M.D.S. AS A SYNTHESIS INTERMEDIATE

The property of easy cleavage of the molecule into two methyl sulphide groups is particularly interesting and permits their introduction into many compounds.

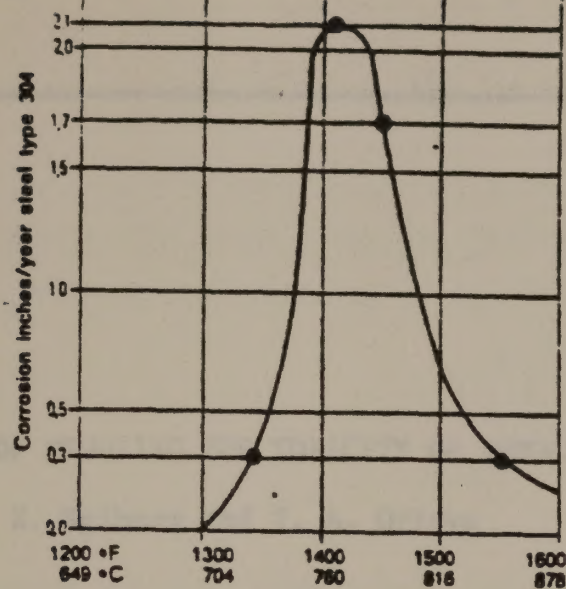
Styrene in presence of iodine and D.M.D.S. yields



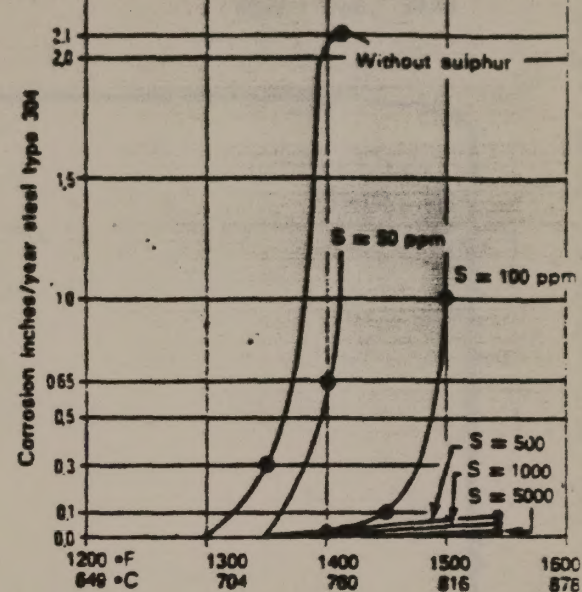
Benzene in presence of AlCl_3 and D.M.D.S. yields



(fig. 1)

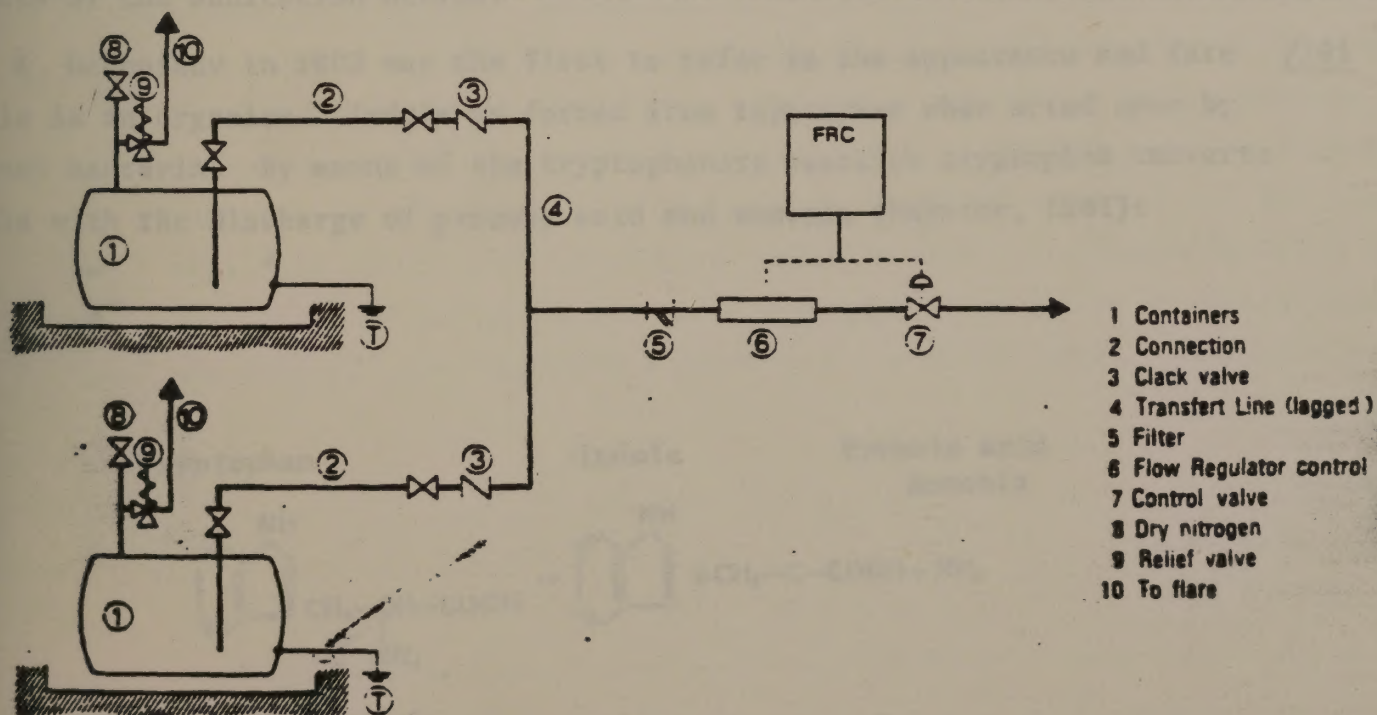
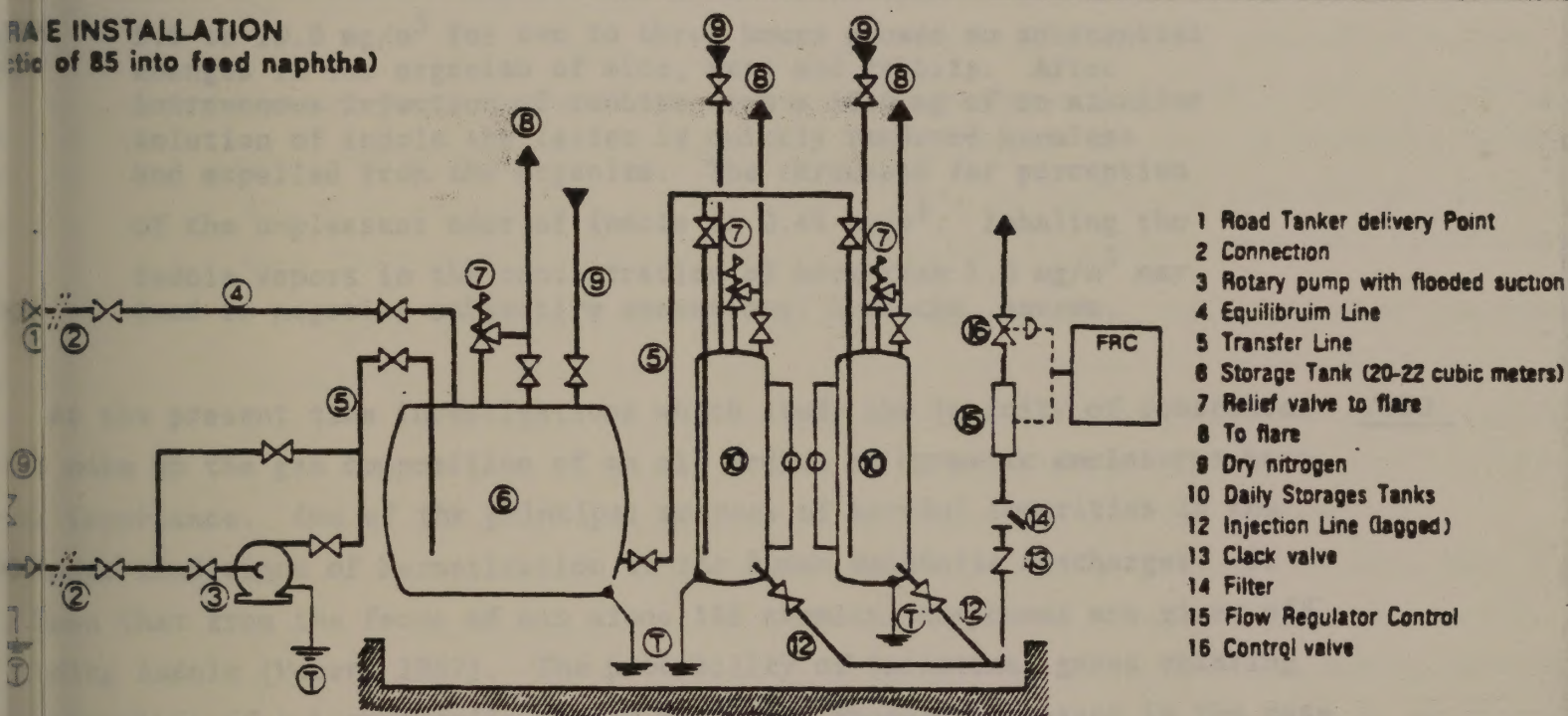


(fig. 2)



RAE INSTALLATION

etic of 85 into feed naphtha)



PROBLEM OF STUDYING THE TOXICITY OF INDOLE

A. K. Sgibnev and T. A. Orlova

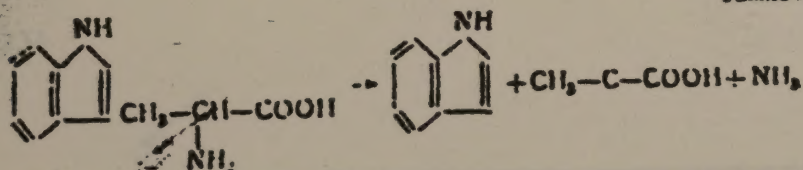
ABSTRACT: Inhalation of indole vapors in a concentration of 9.0 to 10.0 mg/m³ for two to three hours causes no substantial changes in the organism of mice, rats and rabbits. After intravenous injection of rabbits with a 10.0 mg of an alkaline solution of indole the latter is quickly rendered harmless and expelled from the organism. The threshold for perception of the unpleasant odor of indole is 0.45 mg/m³. Inhaling the indole vapors in the concentration of more than 1.0 mg/m³ may lead to negative subjective sensations: headache, nausea.

At the present time investigations which study the toxicity of substances /190 to make up the gas composition of an air medium of hermetic enclosures have great importance. One of the principal sources of harmful impurities in the air under conditions of hermetization is the human metabolic discharges. It is known that from the feces of man alone 196 chemical compounds are given off, including indole (Veber, 1967). The probability of intestinal gases entering the atmosphere of a hermetically sealed enclosure sharply increases in the case of defects of the sanitation device.

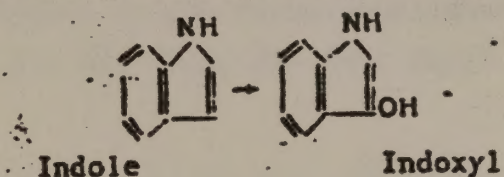
I. I. Mechnikov in 1903 was the first to refer to the appearance and fate /191 of indole in an organism. Indole is formed from tryptophan when acted upon by intestinal bacteria. By means of the tryptophanase reaction tryptophan converts to indole with the discharge of pyruvic acid and ammonia (Mayster, 1961):

Tryptophan

Indole

Pyruvic acid
Ammonia

The greater part of the indole, having been absorbed into the blood from the intestine, enters the liver along the portal vein, where it is rendered harmless, oxidized to indoxyl, and expelled along with the urine in the form of indican.



The daily urine contains from 0.1-38.0 to 40.0-150.0 mg of indican (Gorzheyshi, 1967). The level of indican in the blood is from 0.03 to 0.16 mg percent (Todorov, 1960). A smaller part of the indole is removed with the feces. According to the data of Ury (1904) and Combe (1907) 7-25 mg of indole are removed daily in the feces, and according to the data of Klemmedson (1959) 60-100 mg are removed. 0.013 mg of indole is discharged into the air daily from 100 g of fresh feces (Kustov, Mikhaylov, Poddubnaya, see this collection).

There is information on the effect of indole on the organism of man and animals during parenteral administration and through the gastrointestinal tract in Soviet and foreign literature. Herter (1898), following intravenous injection of dogs with 50-100 ml of 0.1% solution of indole, observed suppression of heart activity, general prostration, narrowing of the pupils, and clonic cramps. After feeding the dogs with indole in a dose of more than 2 g many authors (Baumann, 1886; Jaffe, 1877; Nensky, Siber, Schumov-Simanowsky, 1898) noticed a number of disease phenomena in the animals including hematuria. In 1932 Byungler suggested that indole may play a definite role in pathogenesis of malignant growth. He established that prolonged injection of indole into mice (for six months) causes increase of the hemoporetic tissue in them with an aleukemic blood pattern. The effect of indole on the nervous system was studied by S. D. Bladychko (1911). According to his observations injection of two drops of a 2% solution of indole in olive oil for sixty-three days into the stomach of rabbits caused destructive changes in brain vessels. /1
 The degree of change in the nerve elements corresponded to the affection of the vessels which supplied a given section of the brain. According to the

trial of Herter (1898), the intake of 2 g of indole by man caused headaches and disturbances to sleep. Repeated intake of 1.5 g of indole for four days did not cause disease phenomena.

The data of Tomas and Bek (1967) are further confirmation that inhalation of substances found in the composition of the intestinal gases may cause poisoning of an organism. A ninety-day continuous action of a mixture of indole, hydrogen sulfide, mercaptan and skatole in concentrations equal to an 8-hour PDK on animals (monkeys, mice and rats) led to the death of 99% of the animals. The presence of indole vapors in inspired air has an oppressive effect on the emotional condition of man (Bronshhteyn, 1950). The extremely pleasant odor of indole may cause nausea in persons and other negative subjective sensations (Lazarev, 1954). We did not find any other information in the literature on the effect of indole on the organisms of animal and man after its entrance through the upper respiratory tract and on the threshold for perception of odors. The present study is devoted to the study of these problems.

We used several methodological procedures in order to create the given concentration of the substance. The air was sucked through a column of crystalline indole, through liquid indole and finally through a saturated solution of indole in 50% ethyl alcohol. We managed to create the greatest concentration 0.09-0.01 mg/l by the constant blowing of air through the indole (around 1 g), which was placed on a metallic grid inside a chamber. Increase in the amount of the substance and the length of time air was drawn through it did not affect the concentration of indole vapors in the air. Evidently, for the given concentration the air space in the chamber was completely saturated by the indole vapors.

The concentration of indole in the air was determined by the L. A. Makhov and N. S. Mareyeva method (1962). For this purpose, one liter of air was sucked through 5 ml of 50% ethyl alcohol at a rate of 0.15 l/min. We added 0.04 ml of concentrated acetic acid and just as much sodium acetate to the solution

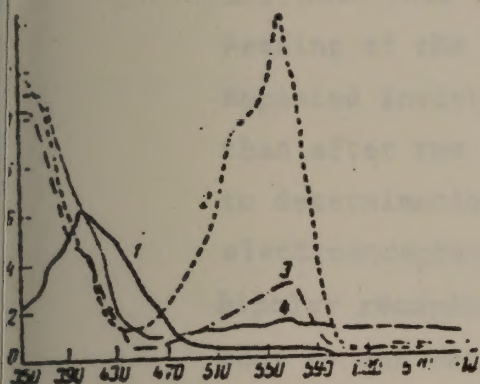
obtained. After five minutes we made a photocalorimetric measurement and a comparison with a standard scale.

We set up two series of tests on twenty mice and fifteen rats in order to study the possibility of acute inhalational poisoning by indole vapor. We inoculated the animals in a hermetic chamber with a volume of 100 l by the static method with an exposure time of two hours. The concentration of indole vapors in the chamber was 0.009-0.01 mg/l. In the first ten-fifteen minutes after beginning of the inoculation both the mice and the rats showed some unrest. Later the behavior and condition of the experimental animals did not differ from the control animals. We did not observe destruction of the mice and rats throughout the fourteen days following inoculation. /1

On the basis of these experiments we figured that indole did not show a pronounced toxic action during acute inhalation poisoning in the test concentrations. Evidently the organism has sufficiently vigorous systems for rendering it harmless.

In order to better understand the supposition that we expressed, we set up test series III on five rabbits weighing 3.5-4.0 kg. The rabbits were subjected to inoculation with an exposure time of three hours at the same concentration of indole with the difference that the substance in the respiration zone was supplied through a special mask. Immediately following the inoculation we determined the amount of indole in the blood plasma of the rabbits according to the Snell method (Snell and Snell, 1937). Blood was taken from an outer vein of the ear. We constructed spectrophotometric curves of the blood plasma with known concentrations of indole in order to determine the amount of indole in the blood: 0.31, 1.25, 6.25 mg %. Analysis of the spectrophotometric characteristics of the plasma showed that the presence of a "peak" in the range of 570 mμ (Figure) is characteristic for indole. The spectrophotometric characteristics of the blood of the inoculated animals did not differ from the intact animals.

In this way, results of this series of tests showed that inhalation of indole in concentrations of 0.009 mg/l did not lead to its accumulation in the blood of the rabbits.



Wavelength, $m\mu$

Spectrophotometric Character-
of Blood Plasma with Varying
Content. 1, Control; 2, 6.25
mg %; 3, 1.25 mg %; 4, 0.31 mg %.

In view of the fact that concentrations of indole larger than 0.009-0.01 mg/l cannot be made, we conducted tests on five rabbits with intravenous administration of indole in order to study the rate at which indole is rendered harmless in an organism. For this purpose 10 mg of alcohol solution of indole were administered to a rabbit through an outer vein of the ear. We took blood samples for analysis from the outer vein of the other ear fifteen minutes, forty-five

and one hour and forty-five minutes following the administration. We found about 0.3 mg % of indole in all of the rabbits in the first portion of blood taken after fifteen minutes. We did not notice any indole in the blood taken after forty-five minutes and after one hour and forty-five minutes. Our investigations of the amount of indican in the blood showed that the amount of it after administration of indole in the blood did not increase. Finally, the indole which was administered not only was quickly rendered harmless but also was removed from the organism of the animals. A direct test would indicate the rate of removal of indole from an organism would be determination of the indican not only in the blood but also in the urine. However, we were not able to obtain urine by means of catheterization of the ear in the rabbits at the same time period at which the blood was removed. Taking into account that indole is quickly rendered harmless and removed from the organism, its unpleasant odor can be considered a principal biologically significant property. We conducted investigations with the participation of fourteen volunteer test subjects in order to determine the threshold perception of the odor of indole by man under laboratory conditions. The subject was placed behind a screen, through which a rubber hose was introduced, which ended in a glass bulb. The bulb inserted in the nose.

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The initial concentration was distributed by the aid of a Zhanne syringe in the necessary amount one time, and a sweet-smelling mixture was fed through the bulb into the nose with a volume of 100 ml at the moment of inspiration. Feeding of the sweet-smelling mixture alternated with feeding of pure air. Repeated investigations were carried out with the test subjects no earlier than after two days. We made recordings of the rate of respiration in addition to determination of the threshold of perception of the odor on the "Al'var" electroencephalograph, the EKG with the second standard lead and the EEG in bipolar recording "forehead - back of the head." Perception of the indole odor by man was as follows:

Concentration, mg/m ³	0.45	0.9	1.12
Number of test subjects	12	13	12
Persons who had a positive response	4	12	6

As can be seen from the data presented four test subjects out of twelve sensed the indole odor at a concentration of 0.45 mg/m³. The absolute majority of the test subjects clearly sensed the indole odor beginning at a concentration of 0.9 mg/m³. A concentration of 0.45 mg/m³ should be considered the threshold for perception of the indole odor by man.

Substantial changes in the recorded physiological indices due to the effect of indole did not appear in concentrations below 0.12 mg/m³. During the action of higher concentrations, immediately following the feeding of a stimulant, two to three inhalations were nonuniform. The nonuniformity of respiration occurred during the action of detected concentrations and evidently was a response to stimulation of the olfactory analyzer. We did not detect any changes on the part of the EKG and EEG during the action of the indole vapors in a concentration up to 9.0 mg/m³. Subjectively the test subjects noticed a very unfavorable odor in concentrations approaching 0.9 mg/m³. Two of them complained of nausea.

Thus, during the one-time inhalation of indole vapors in concentrations of up to 9.0 mg/m³ no essential changes occurred in the organism. However, the unfavorable odor of indole caused negative subjective sensations and some reflex reaction.

Range-Finding Toxicity Data: List VI

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⊗ A table presents acute toxicity and irritation data on more than 300 compounds, accumulated in a continuing program for screening potential commercial products. The standardized experimental methods are described.

DURING the seven years since the appearance of our last communication on the range-finding test,¹ many additional data have become available for presentation. The following Table lists these data under names conforming to the nomenclature used in *Chemical Abstracts*. This may make them unrecognizable to those who know them only by their trade names. For example: ethers of ethylene glycol are sold as CELLOSOLVE solvents, of diethylene glycol as CARBITOL solvents, and of propylene and dipropylene glycol as UCAR solvents. All materials included here are either in commercial production or have been evaluated for commercial potential within the past few years.

As has been stated in earlier communications,¹⁻³ the range-finding test is relied upon only to allow predictions of the comparative hazards of handling new chemicals. Acute toxicity studies, no matter how precisely executed, yield no more than an indication of the degree of care necessary to protect exposed workman or lead to an opinion that certain technically feasible applications of a chemical may or may not eventually be proved safe.

Our last paper¹ included data for epoxy-ethylbenzene. Recently obtained data upon another sample differ somewhat from that previously published. The latest assay yields a single-oral LD₅₀ value of 2.83 ml/kg. Four hours in a concentrated vapor atmosphere caused no deaths among six rats while 1000 ppm inhaled for a similar period of time killed only two of six rats.

Because of minor changes in experimental methods and to eliminate reference to earlier papers in this series,¹⁻³ the methods for ob-

taining the range-finding data are briefly described.

Single oral dose toxicity is estimated by the gastric intubation of groups of five non-fasted, Carworth-Wistar male rats, or in rare instances indicated in the Table of female rats, four to five weeks of age and 90 to 120 grams in weight which have been reared in our own colony and maintained from time of weaning on Rockland rat diet, complete. The dosages are arranged in a logarithmic series differing by a factor of two. Whenever possible, the chemical is administered undiluted. When a lesser concentration is necessary, solution in water or corn oil or suspension in semi-solid agar are the preferred expedients. Occasionally, a 4% solution of TERGITOL Penetrant 7 (essentially an aqueous solution of 25% sodium 3,9-diethyl-6-tridecanol sulfate) has been used as a dispersing agent. Based upon mortalities during a 14-day observation period, the most probable LD₅₀ value and its fiducial range are estimated by the method of Thompson⁴ using the Tables of Weil.⁷ The figures in parentheses show limits of ± 1.96 standard deviations while the absence of parentheses indicates that no range is calculable because no dosage resulted in fractional mortality.

Penetration of rabbit skin is estimated by a technique closely akin to the one-day cuff method of Draize and associates,⁸ using groups of four male albino New Zealand rabbits weighing 2.5 to 3.5 kg. The fur is removed from the entire trunk by clipping, and the dose is retained beneath an impervious plastic film. Dosages greater than 20 ml/kg cannot be retained in contact with the skin. The animals are immobilized during the

24-hour contact period; after which the film is removed and the rabbits are caged for the subsequent 14-day observation period. The LD_{50} is calculated as described above.

Concentrated vapor inhalation consists of subjecting groups of six male or female albino rats to a flowing stream of vapor-laden air. The vapor-air mixture is generated by passing 2.5 liters/minute of dried air at room temperature through a fritted glass disc immersed to a depth of at least one inch in approximately 50 ml of the test chemical contained in a gas-washing bottle. Inhalations are continued for time periods in a logarithmic series with a ratio of two extending from one-fourth to eight hours, until the inhalation period killing about half the number of rats within 14 days is defined. For inhalation periods of ten, five and two minutes in duration, a static technique is used whereby 50 to 100 grams of material, spread over a shallow tray 200 square inches in area, is placed in a 120-liter sealed chamber for at least 24 hours. Six rats are then rapidly introduced by means of a drawer-type cage designed to minimize vapor loss. This static technique, continuing for a maximum of eight hours if necessary, is also employed for mixtures of liquids and for solids. The Table records the longest inhalation period which permitted all rats to survive the two-week observation period. A symbol is used to indicate those few instances when the shortest period attempted caused 100% mortality.

Inhalation of metered vapor concentrations by rats is conducted with flowing streams of vapor prepared by various styles of proportioning pumps.^{9,10} Inhalation periods are usually of four hours' duration unless slight toxicity enforces an eight-hour period. Concentrations recorded are nominal and not analytically verified. They are in an essentially logarithmic series with a factor of two, and the Table records the concentration yielding fractional mortality among six rats within 14 days. Where no fractional mortality was observed, usually both the concentration yielding no mortality and that yielding complete mortality are indicated.

Primary skin irritation on rabbits is recorded in a 10-grade ordinal series and is based upon the severest reaction that devel-

ops on the clipped skin of each of five albino rabbits within 24 hours of the uncovered application of 0.01 ml of undiluted sample or of solutions in water, propylene glycol, or acetone. Grade 1 in the Table indicates no irritation and Grade 2 the least visible capillary injection from the undiluted chemical. Grade 6 indicates necrosis when undiluted and Grade 10 indicates necrosis from a 0.01% solution.

Eye injury in rabbits is recorded in a 10-grade ordinal series and is based upon the degree of corneal necrosis that results from instillation of various volumes and concentrations of chemical, as detailed by Carpenter and Smyth.¹¹ Grade 1 in the Table indicates at most a very small area of necrosis resulting from 0.5 ml of undiluted chemical in the eye. Grade 5 indicates a so-called severe burn from 0.005 ml, and Grade 10 indicates a severe burn from 0.5 ml of a 1% solution in water or propylene glycol.

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Material Studied

Hydrocarbons
Benzene.....
Diethylcyclohexane (mixed isomers).....
Ethylbenzene.....
Fluoranthene.....
2,4,7,8-Tetrahydro-4,7-methanoindene (Dicyclopentadiene).....
m-Xylene.....
Alcohols
1-Butanol.....
Cyclohexanol.....
2-Cyclopentanol.....
2,2-Dimethyl-1,3-butanediol.....
2,2-Dimethylbutanol.....
2,5-Dimethyl-1,2,6-hexanetriol.....
2,5-Dimethylpentanol.....
Dodecylphenol (mixed isomers).....
1-Ethylcyclohexanol.....
2-Ethyl-4-methylpentanol.....
Heptadecanol (mixed primary isomers).....
4-Hexene-1-yne-3-ol.....
2-Hydroxymethyl-norcamphane.....
2-Hydroxymethyltetrahydropyran, (mixed 2,4- and 3,4-dimethyl isomers).....
8-Indanol.....
3-Methylbutanol.....
Methylheptanol (mixed primary isomers).....
4-Methylpentanol.....
1-Naphthol.....
1,3-Pentanediol.....
p-Tert-Pentylphenol.....
2-Propylheptanol.....
Tridecanol (mixed primary isomers).....
2,2,4-Trimethyl-1,3-pentanediol.....
2,2,4-Trimethylpentanol.....
Ethers
Allyl vinyl ether.....

RANGE-FINDING TOXICITY DATA—CONTINUED

Material Studied	Single Oral LD ₅₀ for Rats Ml/Kg	Single Skin Penetration LD ₅₀ for Rabbits Ml/Kg	Concen- trated Vapor Inhalation by Rats Maximum for No Death	Inhalation of Metered Vapor Concentration by Rats			Irritation on Uncovered Rabbit Belly	Corneal Injury in Rabbits
				Concen- tration ppm	Time, hr.	Mortal- ity		
N-Methyl-N-vinylacetamide.....	2.83	1.41	4 hr.	4,000	4	0/5	1	7
p-Tolylmaleimide.....	0.71 (0.48-1.05)*	0.36 (0.22-0.58)*	8 hr.	—	—	—	—	9
Heterocyclic Nitrogen Compounds								
Acrylic acid, 2-(5'-ethyl- pyrid-2'-yl)ethyl ester..	4.92 (3.75-6.46)	2.23 (1.33-3.50)	8 hr.	—	—	—	5	2
1-(2-aminoethyl) piperazine.....	2.14 (1.54-2.99)	0.88 (0.34-2.31)	8 hr.	—	—	—	6	5
1,4-Di-(2-hydroxyethyl) piperazine.....	2.73 (2.68-5.21)	>10	—	—	—	—	3	5
1-[2-(N,N-Dimethylamino) ethyl]-4-methyl- piperazine.....	1.42 (0.96-2.08)	0.39 (0.29-0.53)	8 hr.	—	—	—	6	8
2,6-Dimethylmorpholine..	2.83*	0.71 (0.39-1.30)	4 hr.	4,000	4	0/6	2	7
5-Ethyl-2-methylpyridine- 1-oxide.....	2.00 (1.28-3.13)	1.77	—	—	—	—	2	5
Hexahydro-1,4-diazepine..	2.83*	1.05 (0.75-1.48)	8 hr.	—	—	—	6	9
2-Hydroxyethyl-5-ethyl- pyridine.....	4.29 (3.07-5.98)*	1.78 (0.97-3.26)	—	—	—	—	2	7
1-(2-Hydroxyethyl) piperazine.....	4.92 (3.75-6.46)	>5.0	8 hr.	—	—	—	1	5
Indole.....	1.00 (0.64-1.57)*	0.79 (0.59-1.07)*	8 hr.	—	—	—	—	8
1-Methylpiperazine.....	2.83	1.49 (0.88-2.50)	8 hr.	—	—	—	6	8
1-Phenylpiperazine.....	0.21 (0.13-0.34)*	0.14 (0.08-0.25)	8 hr.	—	—	—	6	9
Piperidine.....	0.52 (0.42-0.64)*	0.82 (0.23-0.43)	15 min. ‡	2,000†	4	0/6	6	9
1-(5,5,7,7-Tetramethyl- 2-octanyl)-2-methyl-5- ethylpyridinium chloride.....	0.54 (0.38-0.75)*	0.071 (0.044-0.11)*	—	—	—	—	7	9
Nitriles								
Acetic acid, 1- cyanovinyl ester.....	0.10 (0.08-0.14)*	0.14 (0.08-0.26)	5 min.	125	4	4/6	4	10
2-Acetoxyisuccinodi- nitrile.....	0.12 (0.10-0.15)*	0.11 (0.06-0.20)*	1 hr.	—	—	—	—	9
Acrylic acid, 2-(2-cyano- ethoxy)ethyl ester.....	1.12 (0.84-1.50)	0.75 (0.51-1.11)	8 hr.	—	—	—	2	5
Acrylic acid, 2- cyanoethyl ester.....	0.18 (0.13-0.24)*	0.22	8 hr.	—	—	—	5	5
Alkyl cyanide.....	0.12 (0.10-0.14)*	1.41	5 min.	250†	4	0/6	2	3
Butyronitrile.....	0.14 (0.10-0.18)*	0.50 (0.27-0.83)	—	1,000	4	5/6	1	2
Chloroacetonitrile.....	0.22 (0.17-0.29)*	0.071	15 min. ‡	250†	4	1/6	2	5
4-Cyanoethoxy-2-methyl- 2-pentanol.....	3.2*	1.5	—	—	—	—	2	5
6-Cyanohexanoic acid, ethyl ester.....	11.2	7.07	8 hr.	—	—	—	3	2
N-Cyanomethylmorpholine, 50%.....	1.23 (0.94-1.61)	0.20 (0.15-0.27)	4 hr.	—	—	—	1	5
5-Cyanopropionic acid, ethyl ester.....	10.3 (8.3-12.8)	—	4 hr.	—	—	—	1	2
Diethylene glycol mono- 2-cyanoethyl ether.....	12.4 (8.3-21.8)*, **	—	8 hr.	—	—	—	2	1
2,4-Dihydroxy-3,3- dimethylbutyronitrile...	0.31 (0.24-0.41)*	0.13 (0.08-0.17)	8 hr.	—	—	—	1	7

Material Studied

Dimethylamino aceto- nitrile.....
2-(Dimethylamino) propionitrile.....
Glycolonitrile, 70%.....
α-Hydroxyisobutyroni- trile.....
Isobutyronitrile.....
Methacrylonitrile.....
3-Methyl-3-butenitrile.....
Trichloroacetonitrile.....
Halogen Compounds
2-Chloro-2-fluoro-1- propene.....
Chloroform.....
6-Chlorohexanoic acid...
6-Chlorohexanoic acid, ethyl ester.....
2-(4-Chlorophenoxy) ethanol.....
Decyl chloride (mixed primary isomers).....
1,1-Diacetoxy-2,2- dichloropropane.....
2-(1,2-Dichloroethyl)- 4-methyl-1,3-dioxolane
2,2-Dichloro-2-methyl- propionaldehyde.....
1,2-Dichloro-2-propanol
2,2-Dichloro-1-propene...
2,2-Dichloropropionic acid.....
2-Fluoro-2-propene-1-ol
1,1,2-Tri (2-chloro- ethoxy)propane.....
1,2,2-Trichloro-1,1,3, 3,3-pentafluoropropane
1,1,1-Trichloropropane...
1,2,2-Trichloropropane...
1,2,2-Trichloropropane...
2,2,2-Trichloropropion- aldehyde.....
2,2,2-Trichloropropionic acid.....
Sulfur Compounds
Acrylic acid, 2-methyl- thioethyl ester.....
2-Acryloxyethyl dimethylsulfonium methyl sulfate.....
Benzene-sulfonic acid.....

Indole with indican and tryptophan were first investigated for carcinogenicity by Stoeber and Wacker in 1910. A few days after a single sub-cutaneous injection of 5% solution of indole in oil in rabbit's ears, atypical epithelial proliferation was observed.

Injection of indole and indican induced tumors, which were identified histologically as carcinomas. Yet, Benthin could not reproduce the observations of these authors using similar experimental conditions. Carvel proved the effects of indole on connective tissue. In his experiments, hens were injected _____ pectorals with 4 ml. of embryonic connective tissue dosed with 0.1% indole. All animals developed spindle-cell sarcomas at the site of injection. An animal died after _____ days with a large tumor (11x9x5 cm) and numerous metastases in the liver, lungs, and peritoneum. Other hens developed tumors after two months that (encompassed?) the whole thorax. The watery exudate of the tumors, run through Berkefeld filter, retained the tumor inducing agent in full strength. Lapidari repeated the experiments of Carvel. He observed benign teratomas and osteosarcomas under the same conditions. Pentimalli obtained negative results in his experiments with indole on five hens. Likewise with 50 rats, Rapisardi could not induce transformation of connective tissue by single intracutaneous application of an indole suspension (indole and distilled _____). These results contradicted the work of Petroff and Krotkina who reported malignant tumors in 8 of 25 rats treated with indole. The animals were intraperitoneally implanted with embryonic connective tissue treated with indole. (Choldin thought that indole had been found to have a predisposing substance.(?)) His hypothesis was based on the observations that white mice painted with tar developed tumors more quickly if pretreated with indole.

Discussion (p. 510)

It should be noted from the evaluation of the literature on indole that the carcinogenic and leukemogenic effects of indole on epithelium, connective tissue and blood forming tissues appears to be dependent on the amount of the substance administered as well as on the distribution over a long time. Also, manifestation of anemia in rabbits was dependent on the lowest dose. Previously cited work by Taylor was the first to indicate the connection of this fact with the anemia causing properties of indoles. Possibly, the negative results in rats of Bernard and Falzoy are the result of the short external application and the low overall dose. Buengeler could establish leukemia (induction effects) in white mice by extending his experiments over eight months and administering a total of 100 mg of indole.

These experiments also show the effectiveness of small doses (20 mg) over longer time. The increased incidence of leukemia in exposed mice (Group I) over the incidence in control (Group I) is statistically significant. (I and II: $t \times 0.013 = 0.149$, $t \approx 11.5$; $1 - \phi(t) < 10^{-6}$. I and III: $t \times 0.015 = 0.2133$; $t \approx 14.2$; $1 - \phi(t) < 10^{-6}$. We must assume that this increase is due to the true leukemogenic activity of indole. A preliminary X-ray treatment (300 r/l or 6×50 r/l) of the mice (Group III) produced no significant increase in leukemia incidence over the control group. (II and III: $t \times 0.1079 = 0.0643$; $t \approx 0.14$; $1 - \phi(t) \approx 0.418$) Epithelial tumors were not produced in our experimental animals. Typical ____ were not observed. The exclusive occurrence of leukemia is remarkable; perhaps it is a peculiarity of the RFH-strain which was not known before. All together, leukemia became manifest between the 60th and 330th day

of the experiment. A characteristic of chronic indole exposure is in the differential formation with the number of injections of the larger decline of mature granulocytes. Extramedullar blood production in the liver could first be detected in animals sacrificed on the 32nd day. Sometimes one finds scarcely any accumulation of pervascularly important lymphocytic cells in normal mouse instititial spaces. Nevertheless, blood formation is not found in adult animals. This marked accumulation, like extramedullar blood formation in the liver, lay around blood vessels and in the Glisson's capsule and was nearly always associated with a high degree of amyloidosis of (spleen ____). Also, these unusual changes in the mice were judged pathologically and stood in connection with the indole injection. With caution, we would like to take up the last result, the correlation of leukemia transformation and the interpretation (of preliminary stages?) of leukemia. Degenerative changes in spleen and liver appear as effects of chronic indole intoxication as well as amyloidosis predominately in the same organs. We are probably dealing with an unspecific reaction by the chronic stimulus of long-lasting effects of indole.

Summary

Myelocytic leukemia was observed in 15% of the white, in-bred mice (spontaneous leukemia rate 1:500) which were sub-cutaneously injected with 20 mg indole and sacrificed after six months. Extensive extramedullar blood formation in different organs and occasional amyloidosis were found in the white mice. The leukemia rate did not increase significantly when indole was injected in conjunction with exposure to 300 r/l or 6 x 50 r/l of X-rays. In both experinmental groups, extensive myelocytic infiltration was found in spleen, liver, and fractionally in kidney and lung. Thus, indole must be considered a leukemogenic substance.

Man könnte das Verhalten der HVL-Funktion nach intravenöser Darreichung von wasserlöslichen Oestrogenen als einen Idealfall des „rebound-effect“ ansehen. Das ist jedoch nicht richtig. Der „rebound-effect“ hat eine längere Zeit anhaltende Einwirkung des peri-

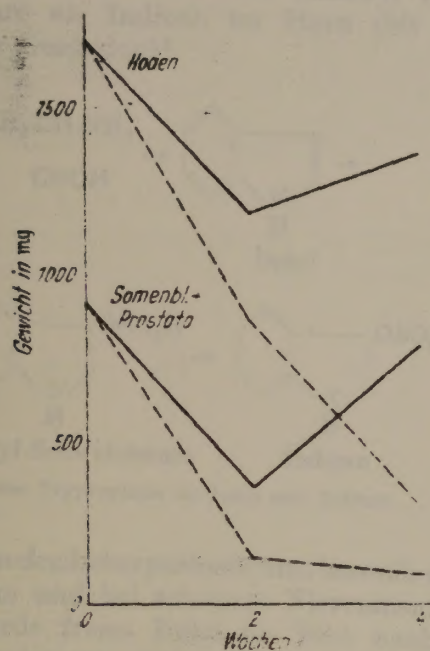


Abb. 5. Verlauf der Hoden- und der Samenblasen- und Prostatagewichte geschlechtsreifer Rattenmännchen, welche einmalig 20 mg Diäthylstilboestrodiphosphat intravenös (ausgezogene Linie) bzw. Dimethoxydiäthylstilboestrol subcutan (gestrichelte Linie) erhalten haben

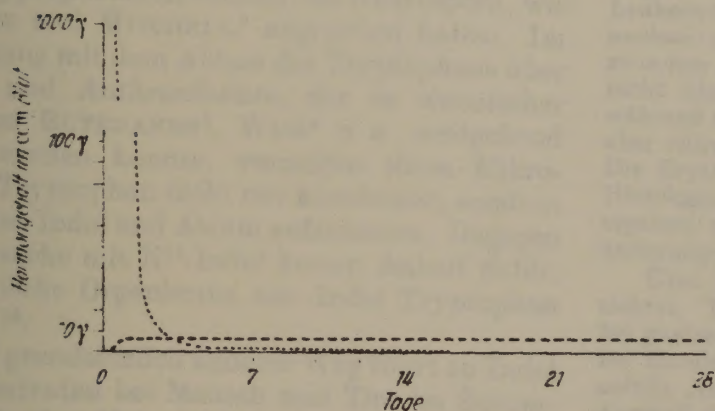


Abb. 6. Wahrscheinlicher Verlauf der Wirkstoffkonzentration im Blut von Rattenmännchen, welche einmalig 20 mg Diäthylstilboestrodiphosphat intravenös (punktierte Linie) bzw. Dimethoxydiäthylstilboestrol subcutan (gestrichelte Linie) erhalten haben

phenen Hormons auf das Hypophysen-Zwischenhirnssystem zur Voraussetzung⁹⁻¹¹. Der „rebound-effect“ wurde als Desensibilisierungs-Effekt 1934 von HOHLWEG¹² entdeckt und beschrieben. Es heißt in der betreffenden Veröffentlichung:

„Nach Aufhören einer längeren Follikelhormonbehandlung erfolgt bei geschlechtsreifen Rattenweibchen eine Zeit verstärkter Sexualcyclen. Auf Grund unserer Anschauungen über die Beziehungen zwischen HVL, Sexualzentrum und KDr kommen wir zu folgender Erklärung dieser Tatsache: Durch die dauernde Follikelhormonzufuhr wird durch das Sexualzentrum die gonadotrope Sekretion des Vorderlappens und dadurch auch die Funktion der KDr gehemmt. Es tritt jedoch nach einiger Zeit eine Gewöhnung des Sexualzentrums an den erhöhten Bluthormonspiegel ein. Wenn dann mit den Injektionen ausgesetzt wird, so ist die hemmende Wirkung einer bestimmten Menge Follikelhormon durch die geringere Empfindlichkeit des Zentrums schwächer als vorher. Es kommt zu einer Steigerung der gonadotropen Sekretion des HVL und dadurch zu einer erhöhten Tätigkeit des Ovars selbst. Durch die Desensibilisierung des Sexualzentrums wird nach Aufhören der Follikelhormonzufuhr eine erhöhte Funktion der KDr ermöglicht.“

In der betreffenden Arbeit wird auch schon darauf hingewiesen, daß diese KDr-Hormonwirkung eine kausale Therapie bestimmter Unterfunktionszustände der KDr ermöglicht. Erst 20 Jahre später wurde dies durch die klinischen Untersuchungen von HECKEL und Mitarbeitern bestätigt^{13, 14}.

Zusammenfassung. Nach einmaliger intravenöser Injektion von wasserlöslichen Oestrogenen (Diäthylstilboestrodiphosphat bzw. Diäthylstilboestrolisulfat) zeigt der Hypophysenvorderlappen normaler erwachsener Rattenmännchen nach 2 Wochen deutliche Überdosierungserscheinungen („Follikelhormon-Hypophyse“ gonadotrop inaktiv), nach 4 Wochen jedoch Kastrationsveränderungen („Kastrations-Hypophyse“ gonadotrop hyperaktiv). Wie diese entgegengesetzten Extreme zustandekommen, wird auf Grund der Beziehungen zwischen Hypophysen-Zwischenhirnssystem und Keimdrüsen und der besonderen Wirkungsart der wasserlöslichen Oestrogene erklärt.

Literatur. ¹HOHLWEG u. DOHRN: Klin. Wschr. 1932, 213. — ²HOHLWEG u. JUNKMANN: Klin. Wschr. 1932, 321. — ³HOHLWEG: Klin. Wschr. 1934, 92. — ⁴HOHLWEG: Klin. Wschr. 1935, 1027. — ⁵HOHLWEG: Klin. Wschr. 1936, 1832. — ⁶SCHOELLER, DOHRN u. HOHLWEG: Klin. Wschr. 1936, 1907. — ⁷HOHLWEG u. CHAMORRO: Klin. Wschr. 1937, 196. — ⁸HOHLWEG: Klin. Wschr. 1937, 586. — ⁹HOHLWEG: Abh. dtsh. Akad. Wiss. Berlin 1953, 34. — ¹⁰HOHLWEG: 2. Symposium der Dtsch. Ges. für Endokrinologie, 1954, S. 156. — ¹¹HOHLWEG: Dtsch. Gesundheitswesen 1956, 245. — ¹²HOHLWEG: Med. Mitt. Schering-Kahlbaum A.G. 6, H. 1, 9 (1934). — ¹³HECKEL and Rosso: J. Clin. Endocrin. 11, 235 (1951). — ¹⁴HECKEL and MacDONALD: Ann. New York Akad. Sci. 55, 725 (1952).

UNTERSUCHUNGEN ÜBER EXPERIMENTELLE LEUKÄMIEN

II. Mitteilung*

Die Indol-Leukämie bei der weißen Maus**

Von

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Das Indol wird im menschlichen Darm aus Eiweiß durch bakterielle Zersetzung gebildet. Schon 1875 wurde es von M. NENČEK¹ bei der Eiweißfäulnis inden

Faeces aufgefunden. Später wurde erkannt, daß dabei Indol aus der Aminosäure Tryptophan entsteht². Das Tryptophan wird durch Einwirkung des in den Colibakterien enthaltenen Ferments Tryptophanase zu Indol abgebaut³. Der genaue Reaktionsmechanismus wurde neuerdings geklärt⁴. Tryptophan wird in einem

* 1. Mitteilung: Bluf 2, 262—271 (1955).

** Auszugweise vorgetragen auf dem VI. Kongreß der Internationalen Gesellschaft für Hämatologie in Boston/USA, 28. August 1956.

Reaktionsschritt auf anaerobem Weg in Indol, Brenztraubensäure und Ammoniak gespalten, Pyridoxal-5-phosphat wirkt als Coferment. Ein Teil des enteral gebildeten Indols wird resorbiert und erscheint schließlich am Ende einer Abbaureihe über Indoxyl und Indoxylschwefelsäure als Indican im Harn (bis zu 30 mg pro die beim Gesunden)⁵.

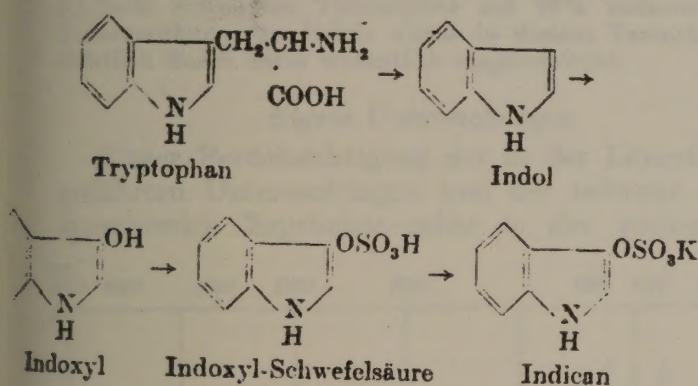


Abb. 1. Der Abbau des Tryptophans zu Indol und Indican

Bei Erkrankungen des Leberparenchyms, besonders dem Coma hepaticum und bei schwerer Niereninsuffizienz (Urämie) wurde freies Indol im Blut nachgewiesen, beim Gesunden war dieses dagegen mit den früheren Methoden nicht nachweisbar⁶.

Von besonderem Interesse ist das Auftreten von Indol im Tryptophanstoffwechsel bei Neurospora, wie HASKINS und MITCHELL⁷ angegeben haben. Im Zusammenhang mit dem Abbau des Tryptophans über Kynurenin und Anthranilsäure, der in chemischer Hinsicht von BUTENANDT⁸, WISS⁹ u. a. weitgehend aufgeklärt werden konnte, vermögen diese Mikroorganismen Tryptophan nicht nur abzubauen, sondern umgekehrt aus Indol und Alanin aufzubauen. Dagegen ergaben Versuche mit N¹⁵-Indol keinen Anhalt dafür, daß der tierische Organismus aus Indol Tryptophan bilden kann¹⁰.

Ein wohl grundsätzlich anderer Weg führt zu Indol zw. Indolderivaten bei Mensch und Tier im Zusammenhang mit der Melaninbildung über das Dioxybenzylalanin (Dopa). Dabei bleibt allerdings die Vorstellung, daß durch Decarboxylierung Dioxy-Indol entstehen soll, zunächst hypothetisch¹¹.

1910 wurde Indol gleichzeitig mit Indican und Tryptophan von STOEGER und WACKER¹² erstmalig auf seine cancerogene Wirkung untersucht. Wenige Tage nach einer einmaligen subcutanen Injektion einer 5%igen öligen Indollösung ins Kaninchenohr wurden atypische Epithelproliferationen beobachtet. Bei der Injektion von Indol und Indican traten Tumoren auf, die histologisch als Carcinome identifiziert wurden. BENTHIN¹³ konnte jedoch die Beobachtungen dieser Tumoren unter ähnlichen Versuchsbedingungen nicht bestätigen. CARREL¹⁴ prüfte den Einfluß von Indol auf Bindegewebe. Bei seinen Versuchen wurden Hühnern 4 cm³ Embryonalgewebe mit einem Zusatz von 0,1% Indol in beide pectorales injiziert. Bei allen Tieren bildeten sich an der Injektionsstelle Spindelzellarkome. Ein Tier starb nach 6 Tagen mit einem Riesentumor (11×9×5 cm) und zahlreichen Metastasen in der Leber, Lunge und Peritoneum. Bei weiteren Hühnern entwickelten sich Tumoren, die sich nach Ablauf von 2 Monaten über den ganzen Thorax ausdehnt hatten. Ein wäßriger Auszug der Geschwülste, durch Kiefeld-Filter filtriert, behielt die tumorezeugende Eigenschaft in voller Stärke. LAPIDARI¹⁵ wiederholte die Versuche mit ARBELS. Er beobachtete unter denselben Bedingungen bei Hühnern benigne Teratome und ein Osteosarkom. PENTIMALLI¹⁶ hatte bei seinen Versuchen mit Indol an 5 Hühnern negative Ergebnisse. Ebenso konnte RAPISARDI¹⁷ bei 50 Ratten, denen Indol in Form einer Suspension (Indol und Aqua dest.) einmal intracutan appliziert worden war, keine Gewebs-

veränderungen feststellen. Diesen Ergebnissen stehen die Arbeiten von PETROFF und KROTKINA¹⁸ gegenüber, nach denen durch Indolbehandlung bei 8 von 25 Ratten maligne Tumoren erzeugt werden konnten. Den Tieren war embryonales Gewebe mit Zusatz von Indol intraperitoneal implantiert worden. CHOLDIN¹⁹ glaubt, in Indol einen die Tumorbildung prädisponierenden Stoff gefunden zu haben. Seine Annahme stützt sich auf Beobachtungen, nach denen bei weißen Mäusen durch Teerpinselung schneller maligne Geschwülste auftraten, wenn sie mit Indol vorbehandelt worden waren.

Als erster prüfte BÜNGELER²⁰ die Wirkung von Indol auf das hämopoetische System. Mäusen wurde in einem Zeitraum von 8 Monaten insgesamt 100 mg Indol/20 g Maus, verteilt auf 80 Injektionen in Form einer 1%igen wäßrigen Lösung subcutan verabfolgt. Die Letalität war sehr hoch, was auf die toxische Anämie zurückgeführt wurde, die mit einem Schwund der blutbildenden Organe einherging. Neben dieser Früh-anämie trat eine sog. Spätanämie auf, die von einer Leukocytose begleitet war. Hierbei kam neben einer Wucherung des myeloischen Gewebes eine deutliche Reduktion der erythropoetischen Reihe zur Beobachtung. Unter dem gesamten Tierrmaterial fanden sich: a) Bei 18 Tieren myeloische Infiltrate in Niere und Lunge, extramedulläre Blutbildungsherde in Leber und Milz. b) Bei 2 Tieren degenerative Veränderungen in Knochenmark, Milz und Leber. Die genannten Veränderungen nahmen mit der Dauer der Versuche zu. c) Bei je einer Maus Lymphadenose (aleukämisch), subleukämische Lymphadenose und Lymphosarkom. d) Vier myeloische Leukämien mit entsprechenden Symptomen und 9 aleukämische Myelosen.

Angeregt durch die Ergebnisse BÜNGELERS injizierte BERNARD²¹ 5 Monate alten Ratten 3 Monate hindurch in Abständen von 8 Tagen je 1 mg Indol intralumbal. Vier Tiere zeigten vom 20. Tage an eine signifikante Vermehrung der Leukocyten mit Polynucleose und Myelocytose. Die Polynucleose schwankte zwischen 50% und 75%, die Myelocytose zwischen 3% und 10%. Die Gesamtzahl der Leukocyten ging nicht über 35000 hinaus. Die myeloische Reaktion blieb während der ganzen Behandlungsdauer bestehen, näherte sich aber einen Monat nach Abschluß der Injektionen der Norm. Die Erythropoese war während des Versuches nicht gestört. Histologische Untersuchungen von Knochenmark und Organen ergaben nach einer 7monatigen Versuchsdauer keine Veränderungen.

Über Indolanämien wurde in der Literatur mehrfach berichtet. TAYLOR²² beobachtete bei Kaninchen, WIGODSKY²³ bei gastrektomierten Hunden und SEBRELL und HUNDLEY²⁴ bei Hunden mit Nicotinsäuremangel nach chronischer Indolzufuhr Absinken von Hämoglobin und Erythrocyten. Das Ausmaß der genannten hämatologischen Veränderungen ging mit der verabfolgten Indolgesamtmenge parallel. Die Anämien bildeten sich jedoch nach Abschluß der Indolzufuhr zurück. Ebenso gelang es FALZOF²⁵ durch Indol bei Ratten Anämien zu erzeugen. Ratten wurden in einem Zeitraum von 50 Tagen 5 mg Indol/die peroral bei einer gleichzeitigen Vitamin B₁₂-freien Ernährung verabreicht. Im Verlauf des Versuches zeigte sich bei den Tieren neben der Anämie eine deutliche Leukopenie, die von einer Leukocytose abgelöst wurde, wobei Neutrophilie und Lymphocytose wechselnd beim gleichen Tier auftraten. Makroskopisch auffallend war die stark vergrößerte und blutreiche Milz sowie im Knochenmark eine hochgradige Linksverschiebung der Granulopoese. BÜNGELERS Annahme der leukämogenen Wirkung des Indols wurde von KAISER²⁶ bestritten. Bei 25 Ratten, denen in einem Zeitraum von 590 Tagen insgesamt 10 g Indol je Ratte mit der Nahrung zugeführt wurde, zeigten sich mäßige Anämie und irreversible Leukocytose, während die Anämie bei Unterbrechung der Indolfütterung verschwand. Die mittlere Lebensdauer der Tiere wurde nicht merklich beeinflusst. Tumoren und Leukämien kamen nicht zur Beobachtung.

Neuere Arbeiten über Indol und verwandte Substanzen befassen sich mit der Frage der Einwirkung dieser Stoffe auf die Tumorraten im Phäno- und Genotyp bei verschiedenen Stämmen von Drosophila. HARTUNG²⁷ fütterte Indolelessigsäure und Adenin zusammen mit toter Hefe bei Tumor- und Nicht-Tumorstämmen von Drosophila melanogaster und an einem Stamm von Drosophila virilis. Mit beiden Substanzen gemeinsam konnten keine tumorösen Neubildungen verursacht werden. Indolelessigsäure allein führte bei einem Tumorstamm zu einer Steigerung der Tumorraten. Bei den übrigen bisher tumorfreien Stämmen traten Melanotumoren auf. HARTUNG möchte das Auftreten bzw. die prozentuale Steigerung der

Melanotumoren mit dem Aminosäurestoffwechsel, speziell von Tryptophan, in Verbindung bringen. PLAINE und GLASS²⁸ verfütterten beim suppressor-erupt-Stamm von *Drosophila melanogaster* Tryptophan und verwandte Stoffe, darunter auch Indol. Die Anzahl der Melanotumoren wurde durch Tryptophan, Anthranilsäure, Indol, Serin, Tyramin und Phenylalanin erhöht. Indol unterschied sich von den übrigen Substanzen durch eine hohe, jedoch sehr inkonstante Tumorate mit einer Schwankungsbreite zwischen 81% und 50%. Bei gleichzeitiger Verfütterung von 0,1% Indol und 5% d,l-Serin wurde die Tumorate auf 26% reduziert. Die Tumorewirkung des Indols wurde in diesem Versuch offensichtlich durch Serin wesentlich eingeschränkt.

Eigene Untersuchungen

Unter Berücksichtigung der in der Literatur angeführten Untersuchungen und der teilweise widersprechenden Ergebnisse sollte in der vorliegenden

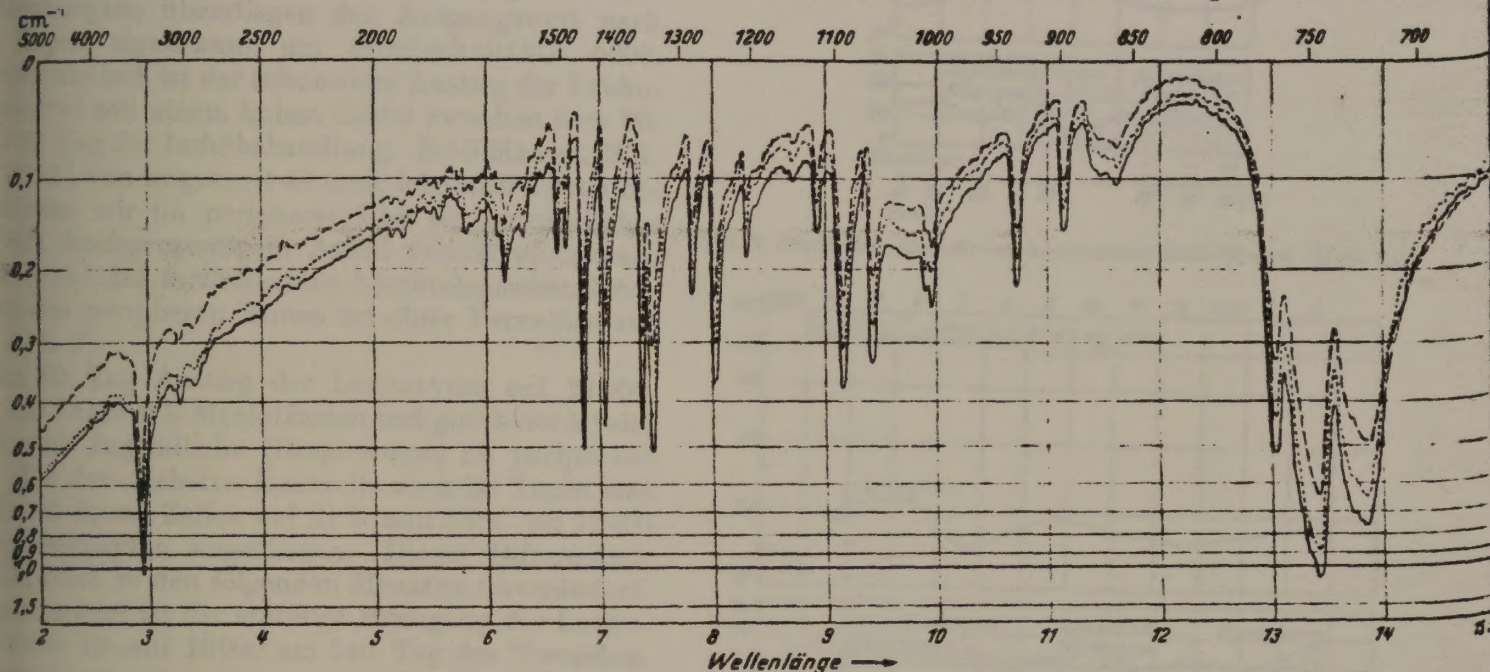


Abb. 2. Infrarotdiagramme von Indolen verschiedener Herkunft

Arbeit die Einwirkung von Indol auf die Hämpoese der weißen Maus geprüft werden. Die Ergebnisse wurden durch eine zweite Versuchsreihe ergänzt, die den Nachweis der potenzierenden Wirkung von zusätzlichen Röntgenganzbestrahlungen zur Aufgabe hatte^{29, 30, 31, 32}.

Methodik

Als Tiermaterial wählten wir weiße RFH-Inzuchtmäuse*, deren Leukämiespontanzrate 1:500 beträgt. Die insgesamt 250 Tiere waren zu Beginn des Versuches 6 Wochen alt und im Mittel 18 g schwer.

Die Einteilung erfolgte in 3 Gruppen: I. Gruppe mit 100 Mäusen als Kontrolle, II. Gruppe mit 50 Mäusen Indol subcutan, III. Gruppe mit 100 Mäusen röntgenvorbestrahlt und nachfolgend Indol subcutan. Die überlebenden Tiere wurden nach 360 Tagen getötet.

Chemisch-analytische Definition des verwendeten Indols. Da uns erst zur Behandlung der Gruppe III synthetisches Indol zur Verfügung stand, haben wir das zur Injektion der Gruppe II verwendete Indol „rein“ (Teerverwertungs AG.) nach Abschluß der Untersuchungen einmal umkristallisiert und mit den Infrarotdiagrammen von synthetischem Indol und dem Eindampfrückstand der Mutterlauge verglichen (Abb. 2). Es traten keine Verschiedenheiten in den Diagrammen auf. Es muß daher angenommen werden, daß die von uns in Gruppe II verwendete Substanz in reiner Form vorgelegen hat.

Bei der Bestimmung der LD₅₀ des schwer wasserlöslichen Indols bedienten wir uns der Methodik von KÄRBER³³. Sie beträgt bei der Lösung von Indol in 50%igem Propylenglykol 4,5 mg/20 g Maus und steigt auf 9,0 mg/20 g Maus an, wenn der Propylenglykolanteil auf 5% reduziert wird. Gleichzeitig

wird damit die Indollöslichkeit auf 0,5% vermindert. Es wechselnde Empfindlichkeit von Mäusen verschiedenen wichtetes des gleichen Stammes, untersucht wurden RFH-Mäuse zwischen 13 und 30 g, gibt es nicht. Für die vorliegenden Untersuchungen wurde eine 1%ige Lösung von Indol in 50%igem Propylenglykol verwendet. Die Aufbewahrung erfolgte unter Lichtschutz, die Erneuerung der Lösung wöchentlich. Die Injektionsdosen betrugen 0,5 mg in 3-4tägigen Abständen bzw. 1 mg wöchentlich in einem Zeitraum bis 140 Tagen. Insgesamt wurden 20 mg Indol je 20 g Maus injiziert.

Die zusätzliche Vorbehandlung der Gruppe III erfolgte mit einer einmaligen Röntgenganzbestrahlung von 300 r bzw. 6×50 r/l innerhalb 9 Tagen³⁴. Um eine vollständige Durchsetzung des Tierkörpers mit der ionisierenden Bestrahlung zu erzielen, verwendeten wir nach einem Vorschlag von SEELENTAG³⁴ harte und stärker gefilterte Therapiestrahlung und auch eine größere Focus-Hautdistanz; die Daten waren: 180 KV, 10 mA, 0,5-1,0 mm Cu-Filter, entsprechend einer Halbwerts-

schicht der Strahlung bei weitgehend kontinuierlicher Gleichspannung von 0,95-1,3 mm Cu. Nach SEELENTAG³⁴ kann damit der Dosisabfall durch Absorption im Körper der Maus höchstens 10% der Einfalldosis betragen. Die Focus-Tierdistanz betrug 100 cm. Damit waren wir in der Lage, auch den geometrisch bedingten Dosisabfall vernachlässigen zu können. Die Inhomogenität des Bestrahlungsfeldes war bei einer Ausdehnung von 25×30 cm auf 10% herabgesetzt. Die Mäuse wurden zur Bestrahlung in 1,8 cm hohe Pappkartons von 15×25 cm eingesetzt. Ein Übereinanderschichten der Versuchstiere war damit unmöglich. Zwei Kartons nebeneinander ergeben das erwähnte Strahlungsfeld. Die Dosis war bei der Versuchsreihe der Röntgenkontrollgruppe und der Gruppe III 300 r/l bzw. 6×50 r/l. Dosierte wurde nach Angaben von SEELENTAG³⁴ nach Zeit, wobei zunächst die Dosisleistung frei Luft im betreffenden Abstand (100 cm) gemessen wurde, zur Kontrolle aber noch ein Dosismesser (Hammer-Dosimeter) mitlief. Bei Dosisleistungen von etwa 9 r/min ergaben sich Bestrahlungszeiten von 23 min bzw. 6×5,5 min. Diese Röntgendosen hatten bei Kontrollgruppen von RFH-Inzuchtmäusen nach einjähriger Beobachtungszeit keine signifikante Erhöhung der spontanen Leukämierate des Stammes zur Folge.

Hämatologische Untersuchungen erfolgten bei allen Mäusen in 4wöchigen Abständen. Die Gesamtdauer des Versuches betrug 360 Tage. Die überlebenden Versuchstiere wurden getötet, sezziert und die Organe und das Knochenmark histologisch untersucht.

Ergebnisse

Gruppe I. Spontanleukämien wurden in der Kontrollgruppe von 100 RFH-Inzuchtmäusen im Verlauf

* Wir danken Herrn Dr. SEELENTAG, Rieder-Institut für Röntgen- und physikalische Therapie der Universität München für die Durchführung der Röntgenbestrahlung.

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* Wir danken den Farbwerken Hoechst AG. für die Überlassung des Mäusestammes RFH und die Förderung unserer Arbeiten.

von 12 Monaten nicht beobachtet. Nach früheren Untersuchungen an einer Kontrollgruppe von 1000 (FH-Mäusen liegt die Spontanrate nach einem Jahr bei 1:500 (Stammzellenleukämie, lymphatische Leukämie).

Gruppe II. Die Anfangsletalität war mit einem Verlust von 20% der Tiere innerhalb der ersten Wochen nach Injektion von durchschnittlich 4 mg Indol je Maus auffallend hoch. Die Gewichtskurve der sterbenden 40 Tiere der Indolgruppe hatte leicht steigende Tendenz, aber nicht über 35 g bei Beendigung des Versuches gegenüber dem Durchschnitt von 40 g der Kontrollen. Eine deutliche Zunahme der Sterblichkeit erfolgte außerdem nach Abschluß der Indoljektion zwischen dem 180. und 240. Tag. Die Gesamtleukocyten überstiegen den Ausgangswert nach 30 Tagen signifikant um durchschnittlich 5000. Charakteristisch ist der schubweise Anstieg der Leukocytenkurve mit einem hohen Gipfel zwischen dem 90. und 150. Tag der Indolbehandlung. Bei 3 Mäusen (201, 225A) von insgesamt 40 noch lebenden Tieren beobachteten wir im peripheren Blut ein leukämisches Bild mit hochprozentigem Anteil von Myeloblasten. Ein Beispiel der fortlaufenden hämatologischen Kontrollen des peripheren Blutes bei einer Versuchsmaus ist Abb. 3.

Am 60. Tag Anstieg der Leukocyten auf 21000, nach 120 Tagen 9% Myeloblasten und gleichviel Myelocyten und Jugendliche (Ringkernige) im peripheren Blut. Bei der nächsten Kontrolle nach 30 Tagen war der Anteil dieser Zellen auf 21% und 23% bei 12400 Gesamtleukocyten angestiegen. Dieses Differentialblutbild blieb in den folgenden Monaten unverändert. Bemerkenswert ist der ständige Rückgang der Leukocytenwerte bis auf 10000 am 240. Tag des Versuches, dem nach vorangegangenen Gewichtssturz und ausgeprägten äußeren anämischen Zeichen spontan der Tod eintrat. Der Verlauf ähnelt dem einer chronischen myeloischen Leukämie. Ähnliche Erscheinungen im peripheren Blut bot die Erkrankung einer weiteren Versuchsmaus, wie es die Abb. 4 veranschaulichen soll.

Bei einer dritten Maus trat schon 35 Tage, nachdem erstmals Myeloblasten im peripheren Blut festgestellt worden, nach akutem Krankheitsverlauf spontan der Tod ein. Drei weitere Mäuse hatten kein leukämisches Blutbild, kamen spontan ad finem, zeigten aber makroskopisch und histologisch leukämische Infiltrationen in verschiedenen Organen. Die Erkrankung dieser Versuchsmäuse war durch plötzlich einsetzende Gewichtsabnahme und hochgradige Anämie charakterisiert. Bei weiteren Mäusen ergaben die histologischen Untersuchungen nach spontanem Tod extramedulläre Blutungsherde in Milz und Leber, die das normale Maß überschritten. Die restlichen 31 Mäuse der Gruppe II wiesen keine wesentlichen Veränderungen im Differentialblutbild auf. Dagegen fanden sich bei manchen Mäusen histologisch Amyloidosen und degenerativen Veränderungen in Leber und Nieren. Eine zusammenfassende Darstellung der pathologischen

Veränderungen der Mäuse in Gruppe II ergeben die Tabellen 1, 2 und 3.

Gruppe III. Die Anfangsletalität nach der einmaligen Röntgenganzbestrahlung mit 300 r und 4 mg Indol betrug 30%. Auch die Aufteilung der Röntgendosis von 300 r/l auf 6 x 50 r/l im Verlauf von 9 Tagen

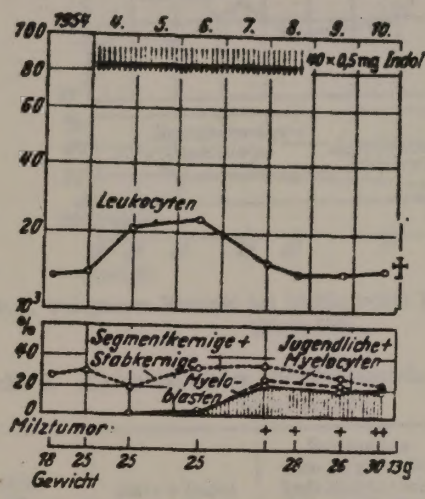


Abb. 3. Peripheres Blutbild bei leukämischer Indol-Myelose (Maus 201)

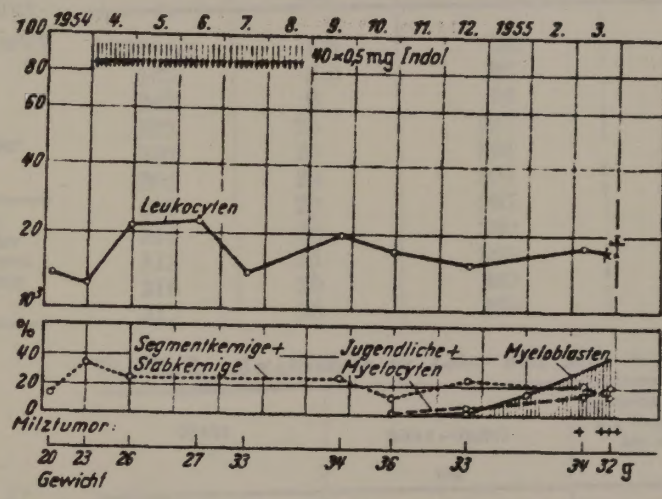


Abb. 4. Peripheres Blutbild bei leukämischer Indol-Myelose (Maus 225A)

änderte bei einem ergänzenden Versuch an der Sterblichkeitsrate nichts. Eine weitere Häufung der Sterblichkeit in dieser Versuchsgruppe bestand zwischen dem 180. und 240. Versuchstag. Die Leukocytenwerte und die Differentialblutbilder bei den insgesamt 70 fortlaufend beobachteten Mäusen finden sich ähnlich wie bei der Gruppe II. Davon zeigen 6 Mäuse nach verschiedenen Beobachtungszeiten ein Auftreten von Myeloblasten und Myelocyten im Differentialblutbild. Beispiele dieser Blutwerte zeigen die Abb. 5 für eine chronische myeloische Leukämie und Abb. 6 für eine akuter verlaufende myeloische Leukämie.

Bei weiteren 8 Mäusen ergaben die Sektionen und histologischen Untersuchungen myeloische Infiltra-

Tabelle 1. Myeloische Leukämien bei Gruppe II

Maus Nr.	Indol mg	Zeitspanne vom Beginn der Indolinjektionen bis zum Exitus Tage	Zeitspanne vom Ende der Indolinjektionen bis zum Exitus Tage	Leukämische Gewebsveränderungen in	Leukämisches Blutbild	Erstmaliges Auftreten von pathologischen Zellen im peripheren Blut nach Tagen
201	20	232	52	Milz, Leber, Niere	+	60
225 A	20	360	180	Milz, Leber	+	330
251	16	140	—	Milz, Leber	+	105
265	20	222	42	Milz	—	—
292	20	260	80	Milz, Leber	—	—
293	20	301	121	Milz, Leber, Niere	—	—

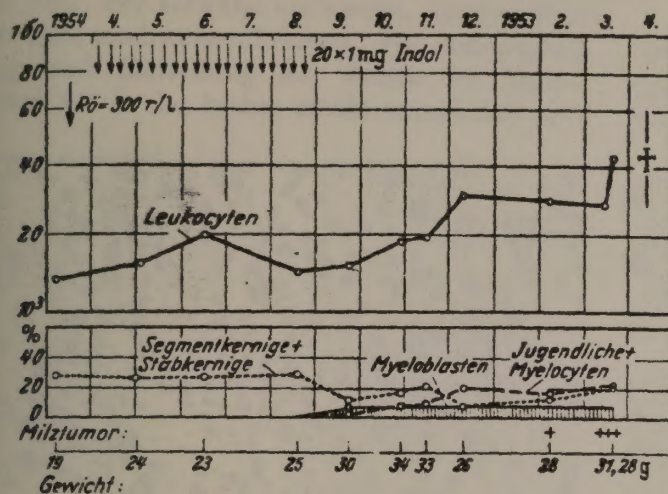


Abb. 5. Peripheres Blutbild bei leukämischer Röntgen-Indol-Myelose (Maus 222)

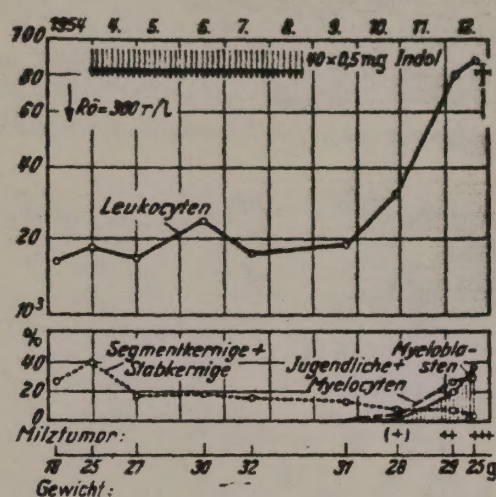


Abb. 6. Peripheres Blutbild bei leukämischer Röntgen-Indol-Myelose (Maus 205)

tionen in verschiedenen Organen. Für alle spontan verendeten Tiere war die Gewichtsabnahme und Anämie kennzeichnend. Eine Übersicht über die RFH-Mäuse der Gruppe III mit myeloischen Leukämien gibt die Tabelle 4. Weitere 11 bzw. 5 Mäuse wiesen bei der histologischen Untersuchung extramedulläre Blutbildungsherde und Amyloidosen auf. Eine Übersicht dieser Mäuse geben die Tabellen 5 und 6.

Tabelle 2. Extramedulläre Blutbildungsherde in der Leber bei Gruppe II

Maus Nr.	Indol mg	Zeitspanne vom Beginn der Indolinjektionen bis zum Exitus Tage	Zeitspanne vom Ende der Indolinjektionen bis zum Exitus Tage
238	14	114	—
1360S	20	185	5
253	20	356	176

Tabelle 3. Amyloidosen der Leber und Milz in Gruppe II

Maus Nr.	Indol mg	Zeitspanne vom Beginn der Indolinjektionen bis zum Exitus Tage
253	20	360 (getötet)
254	20	360 (getötet)
312	20	360 (getötet)

Tabelle 4. Myeloische Leukämien bei Gruppe III

Maus Nr.	300 r + Indol mg	Zeitspanne vom Beginn der Indolinjektionen bis zum Exitus Tage	Zeitspanne vom Ende der Indolinjektionen bis zum Exitus Tage	Leukämische Gewebsveränderungen in	Leukämisches Blutbild	Erstmaliges Auftreten von pathologischen Zellen im peripheren Blut nach Tagen
1369S	12,5	156	—	Milz, Leber	+	150
1372S	13,5	165	—	Milz, Leber	+	155
205	20	330	150	Milz, Leber, Niere, Lunge	+	270
222	20	360	180	Milz, Leber, Niere	+	210
283	20	256	76	Milz, Leber	+	226
323	20	360	180	Milz, Leber, Niere	+	330
1376S	15	30	—	Milz, Leber	—	—
206	20	271	91	Milz, Leber	—	—
219	20	297	117	Milz, Leber	—	—
262	20	188	8	Milz, Leber, Niere	—	—
304	20	272	92	Milz, Leber, Niere	—	—
309	20	360	180	Milz, Leber, Niere	—	—
319	20	360	180	Milz	—	—
20	360	180	180	Milz, Leber	—	—

Tabelle 5. Extramedulläre Blutbildungsherde in der Leber bei Gruppe III

Maus Nr.	300 r + Indol mg	Zeitspanne vom Beginn der Indolinjektionen bis zum Exitus Tage	Zeitspanne vom Ende der Indolinjektionen bis zum Exitus Tage
1377/54	5,5	32	—
103	5,5	32	—
242	9	74	—
203	20	195	15
102	20	201	21
202	20	201	21
219	20	297	117
314	20	360	180
315	20	360	180
316	20	360	180
317	20	360	180

Tabelle 6. Amyloidosen in Leber und Milz bei Gruppe III

Maus Nr.	300 r + Indol mg	Zeitspanne vom Beginn der Indolinjektionen bis zum Exitus Tage
101	5,5	32
S 1377/54	5,5	32
S 1369/54	11,5	156
S 1372/54	13,5	165
320	20	360 (getötet)

Knochenmarksuntersuchungen

Soweit eine Analyse des Knochenmarks bei den spontan verendeten Mäusen möglich war, zeigten die Tiere mit leukämischen Veränderungen in Blut und Geweben einen hochprozentigen Anteil von Myeloblasten und Übergangsformen bis zu den Myelocyten im Markausstrich. Bei der Auszählung der zelligen Elemente des Knochenmarks kamen wir im Durchschnitt auf etwa 75% unreife Zellen der myeloischen Reihe, gegenüber 30% bei Kontrolltieren. Ähnliche Verhältnisse fanden wir bei den überlebenden und nach 360 Tagen getöte-

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Mäusen, die gleichfalls leukämische Veränderungen Blutes bzw. der Gewebe aufwiesen. Leeres Mark
en wir nicht nachweisen können. Die Auszählung,
ennung und Einteilung der Zellen im Mäuse-
chenmark ist in der bisher erschienenen Literatur

Histologische Untersuchungen Gruppe II*

Histologisch fanden sich in den Lebern leukämisch
erkrankter Mäuse hochgradige myeloische Metaplasie
im Sinne leukämischer Infiltrate, daneben Erweite-
rung der intraacinären Capillaren, die mit myeloischen



7. Maus Nr. 251. Myeloische Metaplasie der Leber bei leukämischer
Indol-Myelose. (Abbildungsmaßstab 88:1 auf dem Film.
4mal nachvergrößert. H.-E.-Färbung)

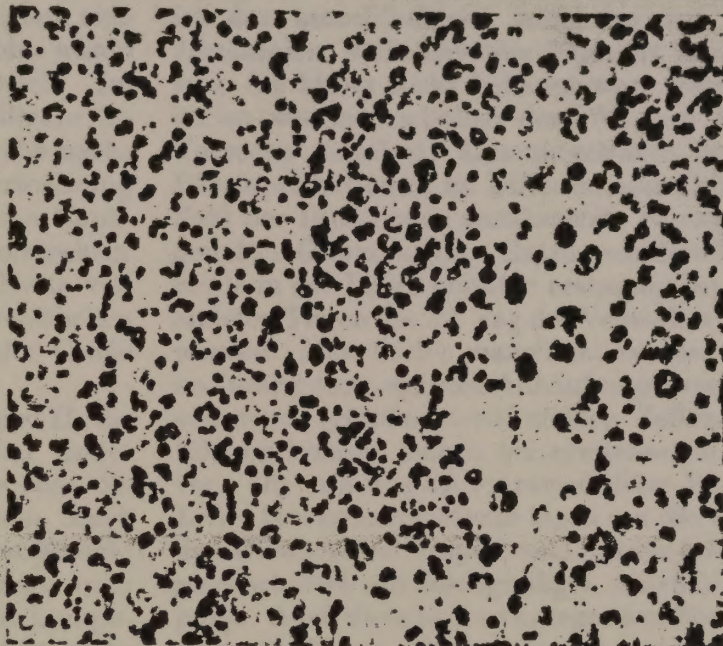
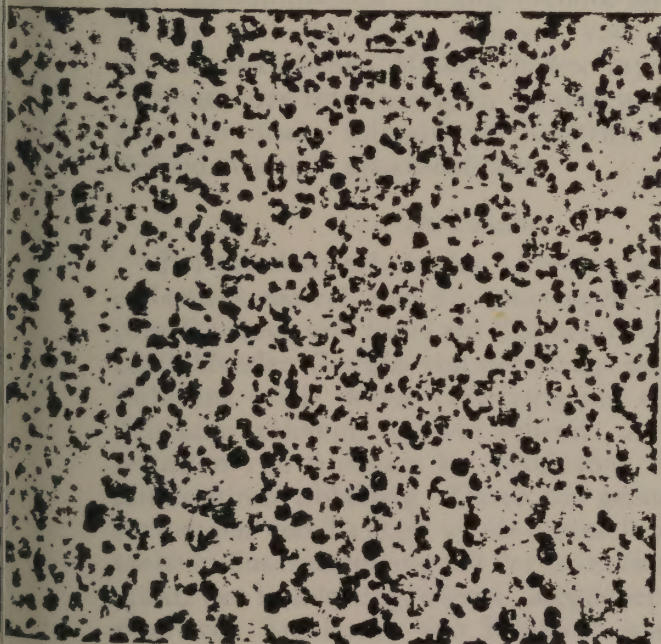


Abb. 9. Maus Nr. 222. Myeloische Metaplasie der Leber mit hochgradiger
Atrophie der Leberzellbälkchen bei leukämischer Röntgen-Indol-Myelose.
(Abbildungsmaßstab 88:1 auf dem Film. 4mal nachvergrößert.
H.-E.-Färbung)



8. Maus Nr. 251. Myeloische Metaplasie der Milz bei leukämischer
Indol-Myelose. (Abbildungsmaßstab 88:1 auf dem Film.
4mal nachvergrößert. H.-E.-Färbung)

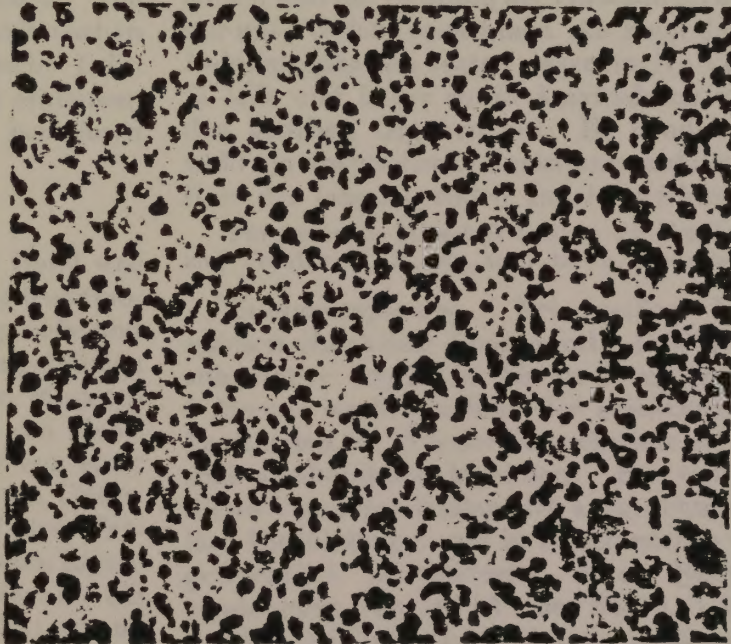


Abb. 10. Maus Nr. 222. Myeloische Metaplasie der Milz bei leukämischer
Röntgen-Indol-Myelose. Keine Unterscheidung zwischen Follikeln und
Pulpa möglich. (Abbildungsmaßstab 88:1 auf dem Film.
4mal nachvergrößert. H.-E.-Färbung)

verschiedener Weise erfolgt, daß wir auf Angabe
absoluten Werten verzichten.

Sektionsergebnisse

Die leukämischen Erkrankungen bei unseren Ver-
stärkungen zeichneten sich durch teilweise extreme
Vergrößerungen aus. Die Milz der erwachsenen
Mäuse hat durchschnittlich eine Länge von 15 mm,
eine Breite von 3 und eine Dicke von 2 mm. Bei
leukämischen Mäusen steigen diese Maße bis auf 50 mm,
40 mm und 5 mm an, die Gewichte der pathologisch
veränderten Organe bis auf 4,5 g.

Zellelementen angefüllt sind (Abb. 7). Ähnliche Ver-
änderungen der Leber fanden wir in den Fällen von
aleukämischer Indol-Myelose. Normalerweise soll in
der Leber erwachsener Mäuse keine Blutbildung vor-
kommen.

In den Milzen leukämischer Tiere ließ sich eine
eindeutige myeloische Metaplasie mit Verschwinden
der Lymphfollikel nachweisen (Abb. 8). Auch bei
aleukämischer Indol-Myelose fanden sich in den Milzen
typische myeloische Metaplasie der Milzpulpa. Bei

* Wir danken Herrn Dozent Dr. med. W. BENNETT, Frankfurt a. M.,
höchst, für die Anfertigung und Beurteilung der histologischen Präparate.

Kontrollmäusen waren die Follikel zahlreich und überwogen gegenüber der roten Pulpa.

Teilweise konnten in Nieren und Lungen typische leukämische Infiltrationen nachgewiesen werden.

Histologische Untersuchungen Gruppe III

In den Lebern aleukämischer und leukämischer Röntgen-Indol-Leukämien zeigte sich histologisch eine ausgedehnte myeloische Metaplasie. Die Bilder waren praktisch mit denen der Gruppe II identisch. Im einzelnen ließen sich die myeloischen Infiltrate im Interstitium und im periportal Bindegewebe nachweisen, es bestand weiterhin eine starke Vermehrung myeloischer Zellelemente in den intraacinar Capillaren. Teilweise machte es Mühe, die Leberstruktur überhaupt noch zu erkennen, da nur noch Reste von Leberbälkchen vorhanden waren. Die Leberepithelien sind größtenteils verquollen, die Kerne in der Größe sehr unterschiedlich (Abb. 9).

In der Milz imponiert, wie auch bei Gruppe II, die myeloische Metaplasie der Milzpulpa. Man findet meistens nur noch ganz vereinzelte Lymphocyten, die meisten Zellen sind der Myelopoese zuzurechnen. Auch fanden wir Infarktbildungen mit Vernarbungen. Manchmal ähnelten die histologischen Bilder der Milzen mehr Knochenmarksschnitten: eine Gliederung in Lymphfollikel und Sinus bzw. Reticulum war nicht mehr möglich (Abb. 10).

Auch bei der Gruppe III fanden sich die gleichen typischen leukämischen Organveränderungen wie bei den aleukämischen Röntgen-Indol-Myelosen. Die Nieren und teilweise Lungen von leukämischen und aleukämischen Mäusen ließen myeloische Infiltrationen des intertubulären Bindegewebes erkennen. Eine chronische interstitielle Nephritis ist bei diesen Befunden sicher auszuschließen.

Diskussion

Bei der Auswertung der Literatur über Indol war es bemerkenswert, daß die cancerogene und leukämogene Wirkung von Indol auf Epithel, Bindegewebe und blutbildenden Gewebe von der Menge der zugeführten Substanz sowie deren Verteilung auf einen längeren Zeitraum abhängig zu sein scheint. Auch die Manifestation von Anämien bei Kaninchen war von einer Mindestdosis abhängig. Durch die genannten Untersuchungen von TAYLOR wurde erstmals auf diese Tatsache in Zusammenhang mit der anämisierenden Eigenschaft des Indols hingewiesen. Möglicherweise sind die negativen Ergebnisse von BERNARD und FALZOV an Ratten in der kurzdauernden Applikation und der kleineren Gesamtdosis von Indol begründet. BÜNGELER konnte bei der Ausdehnung seiner Untersuchungen über 8 Monate an weißen Mäusen und einer Verabfolgung von insgesamt 100 mg Indol dessen leukämieerzeugende Wirkung nachweisen.

Die vorliegenden Untersuchungen zeigen die Wirksamkeit auch kleinerer Gesamtdosen (20 mg) bei genügend langer Beobachtungszeit. Die zahlenmäßige Differenz der mit Leukämie befallenen Mäuse der Gruppe II gegenüber der Spontanrate der Kontrollgruppe (I) und zwischen Gruppe I und III ist statistisch signifikant. (I und II: $t \times 0,013 = 0,149$; $t \approx 11,5$; $1 - \varphi(t) < 10^{-6}$. I und III: $t \times 0,015 = 0,2133$; $t \approx 14,2$; $1 - \varphi(t) < 10^{-6}$). Wir müssen daher annehmen, daß dem Indol echte leukämogene Eigenschaften zu-

kommen. Eine Röntgenvorbehandlung (300 r/l bzw. 6×50 r/l) der Versuchstiere bewirkt gegenüber Gruppe II keine signifikante Zunahme der Leukämiehäufigkeit. (II und III: $t \times 0,079 = 0,0643$; $t \approx 0,11$; $1 - \varphi(t) \approx 0,418$). Epitheliale Geschwülste sind bei unseren Versuchstieren nicht aufgetreten. Typisch Lymphadenosen wurden nicht beobachtet. Erstaunlich ist das ausschließliche Auftreten von myeloischen Leukämien, vielleicht eine Eigenart des RFH-Stammes, die bisher nicht bekannt war. Sämtliche Leukämien wurden zwischen dem 60. und 330. Tag des Versuchs manifest. Charakteristisch für chronische Indolapplikation ist im Differentialblutbild der mit der Zahl der Injektionen zunehmende Rückgang der angereiften Granulocyten. Extramedulläre Blutbildung herde in der Leber konnten erstmalig bei spontan verendeten Tieren am 32. Tag des Versuches nachgewiesen werden. Man findet manchmal bei der Normalmaus im Interstitium spärlich Anhäufungen von perivascular gelegenen lymphocytenähnlichen Zellen. Eine Blutbildung kommt jedoch bei erwachsenen Tieren nicht vor. Die von uns als extramedulläre Blutbildung der Leber bezeichneten Herde lagen um die Gefäße und in der Glissonschen Kapsel und waren fast immer vergesellschaftet mit hochgradiger Amyloidose der Milzpulpa. Auch diese in der vorliegenden Form bei Mäusen ungewöhnlichen Veränderungen werden als pathologisch und in Zusammenhang mit den Indolinjektionen stehend gewertet. Wir möchten die letzteren Befunde den leukämischen Organveränderungen gegenüberstellen und die Deutung als Vorstadien einer Leukämie nur mit Vorsicht vornehmen. Als Folge der chronischen Indolintoxikation traten degenerative Veränderungen in Milz und Leber sowie Amyloidosen vorwiegend in den gleichen Organen auf. Es handelt sich hierbei wohl um unspezifische Reaktionen auf den chronischen Reiz der langdauernden Indoleinwirkung.

Für wertvolle Mitarbeit danken wir Fräulein Dr. M. LEY und Fräulein E. ZABEL, med.-techn. Assistentin.

Zusammenfassung. Bei weißen RFH-Inzuchtmäusen (Leukämie-Spontanrate 1:500) traten nach subcutaner Injektion bis zu 20 mg Indol spätestens 6 Monate nach Abschluß der Injektionen myeloische Leukämien bei 15% der Versuchstiere auf (leukämische und aleukämische Myelosen). Bei weiteren Mäusen dieses Versuches fanden sich ausgedehnte extramedulläre Blutbildungsherde in verschiedenen Organen und gelegentlich Amyloidosen. Nach Röntgen-Ganzbestrahlungen von 300 r/l oder 6×50 r/l und anschließenden Indolinjektionen (insgesamt 20 mg Indol) stieg die Leukämierate im Vergleich zur Versuchsgruppe, die ausschließlich Indol erhalten hatte, nicht signifikant an. In beiden Versuchsgruppen fanden sich in Milz, Leber und teilweise in Nieren und Lungen ausgedehnte myeloische Infiltrationen. Danach muß das Indol als leukämogene Substanz betrachtet werden.

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DIE FREIEN AMINOSÄUREN DES LIQUORS BEI DER MULTIPLLEN SKLEROSE

Von

H. BAUER und P. BOESCHE

Aus der „Stiftung zur Erforschung der spinalen Kinderlähmung und Multiplen Sklerose“
und der Neurologischen Universitätsklinik Hamburg-Eppendorf (Direktor: Prof. D. H. PETTE)

Von den zahlreichen Versuchen, die Multiple Sklerose durch serologische bzw. humoral-chemische Veränderungen diagnostisch zu erfassen, haben sich bisher vornehmlich die Untersuchungen der Liquorproteine hinsichtlich ihrer Gesamtmenge, Einzelfractionen und Verhalten in der Kolloidkurve als praktisch nachweisbar erwiesen. Der bekannte Befund der „albumin-kolloidalen Dissoziation“ — eine Störung der Oidstabilität der Liquorproteine (pathologische Stix-, Goldsol-, HCl-Collargolkurve) bei fehlender oder nur unwesentlicher Veränderung ihrer Gesamtmenge — konnte durch die elektrophoretischen Befunde der letzten Jahre erweitert werden, so daß wir heute in einer selektiven Vermehrung der γ -Globuline bei normalem oder nur wenig erhöhtem Gesamteiweiß ein kennzeichnendes, allerdings nur in rund der Hälfte aller Fälle vorkommende Liquorsyndrom der Multiplen Sklerose sehen.

Die Feststellung, daß im Liquor kennzeichnende Proteinveränderungen auftreten, bei welchen gleichzeitige Eiweißverschiebungen im Blutserum fehlen oder nur andeutungsweise vorhanden sind, ließ die Frage aufkommen, ob nicht auch im Bereich der Eiweißspaltprodukte kennzeichnende Liquorveränderungen nachzuweisen seien. Eine Erfassung und Differenzierung der Liquorpeptide scheiterte bisher an technischen Schwierigkeiten. Mit der zweidimensionalen Papierchromatographie lassen sich die Aminosäuren des Liquor jedoch gut erfassen und charakterisieren. Dabei ist der Einwand naheliegend, daß die im Vergleich zu den Proteinen kleinen Aminosäuremoleküle die Blut-Liquorschranke relativ frei passieren könnten und daß somit eine von den Serum-Aminosäuren abweichende Zusammensetzung der Liquor-Aminosäuren nicht zu erwarten sei. Daß dies jedoch nicht der Fall ist, zeigt das Verhalten von Glutamin und Glutaminsäure: beide Substanzen unterscheiden sich hinsichtlich der Molekülgröße nur unwesentlich (Mol.-Gew. 147:146); trotzdem ist die Blut-Hirn-Schranke für Glutaminsäure nahezu unpassierbar, während Glutamin die Schranke frei passieren kann (WEIL-ALHERBE²⁹, WAELSCH²⁵). Dementsprechend ist die Konzentration von Glutamin im Plasma (5,78 mg-%) und Liquor (7,35 mg-%) vergleichbar, während der Glutaminsäuregehalt des Plasmas (3,41 mg-%) erheblich höher liegt als derjenige des Liquors (0,8 mg-%) (TUDWIG¹³). Die Folgerung liegt nahe, daß der Li-

quor eine charakteristische, vom Plasma abweichende Aminosäurezusammensetzung hat. Darüber hinaus kann gefolgert werden, daß ein Suchen nach charakteristischen Veränderungen der Aminosäuren besonders bei solchen Erkrankungen gerechtfertigt erscheint, die nicht mit massiven Störungen der Blut-Liquorschranke einhergehen. Solche Voraussetzungen finden sich bei der Multiplen Sklerose.

Der Versuch einer direkten Trennung der freien Aminosäuren des Liquors in der Hochspannungselektrophorese-Apparatur nach WERNER³⁰ (57 V/cm, 15 mA, 4 Std Laufzeit, Temperatur der Kühlsole -15°C , Ameisensäure-Essigsäure Puffer pH 1,9) ergab keine befriedigenden Resultate. Bei Auftragen von 1 ml mittels Methanol-Aceton enteiweißtem, vakuum-eingeengtem Liquor traten stereotyp 8 Flecke in der Wanderungsposition bekannter Aminosäuren auf (Abb. 1), deren Identifizierung im eindimensionalen Lauf der Hochspannungselektrophorese jedoch nur teilweise möglich war.

Die Aufarbeitung in der Hochspannungselektrophorese ergab eine sehr auffällige Besonderheit des Liquors: im Gegensatz zu dem ähnlich aufgearbeiteten Serum, den Serumhydrolysaten und den Hydrolysaten von Hirngewebe fand sich im Liquor mit Regelmäßigkeit die mit Abstand stärkste Bande im Wanderungsbereich von Glutamin und Glutaminsäure. Bemerkenswert ist, daß nicht hydrolysierte Hirnhomogenisate nach Enteiweißung und Einengung des Überstandes ebenfalls die auffällig starke Bande im Bereich von Glutaminsäure-Glutamin (die bei dem verwendeten pH die gleiche Wanderungsgeschwindigkeit aufweisen) zeigten (Abb. 1). Aus diesen Befunden kann gefolgert werden, daß der Liquor hinsichtlich seiner Zusammensetzung an niedermolekularen ninhydrin-positiven Substanzen eine größere Ähnlichkeit mit Hirngewebe als mit Serum aufweist.

Methoden

Zur Enteiweißung der Liquorproben wurde eine Unterdruckfiltration in Anlehnung an das Verfahren von MIES¹⁶ vorgenommen. Da dadurch in nicht jedem Fall eine vollständige Beseitigung des Eiweißes gegeben war, wurde dem Filtrat die 10fache Menge Methanol/Aceton (3:1) zugegeben, das Ganze geschüttelt und über Nacht bei 4°C stehen gelassen. Meist setzt sich dann ein feiner Niederschlag ab. Der Überstand wird vom Niederschlag durch Filtration mit einem Schleicher & Schüll- (S. + S.) Filter 589³ getrennt und auf dem Wasserbad unter CO_2 zur Trockne eingengt.

SCIENTIFIC LITERATURE REVIEW
OF PYRROLE AND RELATED SUBSTANCES
IN FLAVOR USAGE

VOLUME I

INTRODUCTION AND SUMMARY,
TABLES OF DATA AND BIBLIOGRAPHY

FEMAM

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Copy 1

Multiple Dose Oral Feeding Studies

No	Substance	Species	Dose (mg/kg/day)	Duration	Comments	Ref No	Estimated per capita Daily Intake
2	Pyrrolidine	Rat	8.6 with 17.6 NaNO ₂ ¹	75 weeks	After a total of 100 weeks, no significant differences in comparison with controls with respect to survival rate, tumor incidence and tumor type were seen	104	<0.001 mg ₅ ($<2 \times 10^{-5}$ mg/kg)
4	Indole	Rat	375 & 500 ²	9-21 days	Growth depression which was reduced or reversed when indole additions were supplemented with either methionine, cysteine, cystine or glutathione for following 15-27 days	374a	0.00425 mg (7×10^{-5} mg/kg)
		Rat	375 & 500 ²	18-36 days	Growth depression which was not effectively reversed when indole additions were supplemented with various sulfur containing compounds for 6-30 days	374a	
		Rat	375 & 500 ²	15-21 days	Growth reduction not reduced when indole additions were supplemented for following 21-51 days by various sulfur compounds	375	

000014

No	Substance	Species	Dose (mg/kg/day)	Duration	Comments	Ref No	Estimated per capita Daily Intake
4	Indole (cont)	Rat	250 ³	From day 4 to 20 of gestation	Maternal growth reduced on 8% but not 25% casein diet; no significant findings on day 15, 17 or 19 of gesta- tion when examining fetal and placental weight; no evidence of anomalies or resorptions ascribed to indole administration	210	
		Rat	277	3 weeks	Reduced bodyweight and growth rate	202	
		Rat	390 & 632	3 weeks	Reduced food intake, body- weight and growth rate	202	
		Rat	62.5 ³	28 days	No adverse effects	289	
		Rat	125 ³	28 days	Reduced hemoglobin & hema- tocrit values	289	
		Rat	250 ³	28 days	Food intake and weight gain decreased progressively	289	
		Rat	500 & 1000 ³	28 days	Food intake and weight gain decreased progres- sively; coarse tremors, pallor of ears, ataxia, frank anemia and mortality 1/6 & 3/6, respectively, be- fore experiment's comple- tion	289	

<u>No</u>	<u>Substance</u>	<u>Species</u>	<u>Dose</u> <u>(mg/kg/day)</u>	<u>Duration</u>	<u>Comments</u>	<u>Ref No</u>	<u>Estimated</u> <u>per capita</u> <u>Daily Intake</u>
4	Indole (cont)	Rat	250 ³	26 days	Significant growth retardation which was eliminated with dietary supplements of 0.5, 0.75 or 1.0% methionine	289	
		Rat	250 ³	33 days	Significant growth retardation eliminated with dietary supplements of 0.125-0.5% methionine	289	
		Rat	250 ³	4 months	Growth completely inhibited during 3/4 months	374a	
		Rat	125 ³	7 months	Weight gain inhibited as much as 80%	374a	
		Rat	188 ³	10 months	Little or no growth during 8/10 months with only 50% weight gain other 2 months	374a	
		Rat	100	460 days, 30 days basal ration alone	Poor weight gain, hemoglobin levels reduced during treatment but normal during rest period and after cessation of treatment; reduced erythrocyte levels at 100 mg/kg were normal during rest period but depressed again and remained that way after treatment with 200 mg/kg; leukocyte levels increased during treatment and after cessation; blood cell analysis showed no evidence of leukemia	166	
			200	then 100 days			

000016

No	Substance	Species	Dose (mg/kg/day)	Duration	Comments	Ref No	Estimated per capita Daily Intake
4	Indole (cont)	Guinea pig	115 then 77	21 days then 19 days	Growth retardation	79	
5	Skatole	Rabbit	30/dose ⁴	2 times weekly for 21-40 doses	Increased adrenal weights; histopathology-hypertro- phy of adrenal gland but not of cortex	31	
6	Methyl 2-pyrrolyl ketone	Rat	87.5(M) & 86.3(F)	13 weeks	No adverse effects	270	0.00012 mg (2 x 10 ⁻⁶ mg/kg)
10	N-Furfurylpyrrole	Rat	12.2	90 days	No adverse effects	94	0.00006 mg (1 x 10 ⁻⁶ mg/kg)

1. A total of 1.8 and 3.7 g of pyrrolidine and NaNO₂, respectively, were consumed in the drinking water over the 75 week period. Average daily intakes were calculated and an assumed bodyweight of 0.4 kg was used in calculating approximate daily dose levels.
2. These intake figures are based on ppm in the diet using the assumption that for a weanling rat 10 ppm is equivalent to 1 mg/kg/day.
3. These intake figures are estimates based on ppm in the diet using the assumption that 20 ppm is equivalent to 1 mg/kg/day.
4. Rabbits were dosed on the average of twice weekly at a level of 30 mg/kg/dose for a total of 21-40 doses.

000017

Name of Substance: INDOLE [4]

Reference No.: 219 (Mirsky, I.A., et al. Proc. Soc. Exp. Biol. Med. 1957)

Indole and rat (Carworth, M) liver extracts were incubated *in vitro* at 37° for 30 minutes in a Sorensen's M/15 phosphate buffered medium containing a mixture of I¹³¹ labeled and unlabeled insulin. Indole concentrations of either 0.1, 0.5, or 0.25M inhibited insulin destruction by fresh extracts by factors of 25.6±1.7, 23.3±0.9, and 13.5±2.9%, respectively.

Reference No.: 312 (Sharlit, H. Arch. Derm. Syph. 1948)

Indole was added to the diet of rats for approximately 2.8 weeks resulting in a total intake of 1.8 mg for each rat. Urine excretions were pooled for about 5 weeks prior to treatment, during treatment (i.e., 2.8 weeks), and 6 weeks afterward for a total of 14 weeks. Pre-dosing levels of urinary indican (indoxyl potassium sulfate) ranged from 7.5-11.5 mg/kg bodyweight. Indican levels at the initiation of indole treatment averaged 10 mg/kg and reached maximum values of 21 mg/kg at the completion of treatment. Post-dosing urinary indican levels rapidly declined to an average value of 6.5 mg/kg.

Reference No.: 79 (Ekman, B. K. Fysiograf. Sallakapet Lund Forhandl. 1947)

Five guinea pigs were given daily a 20 mg oral dose of indole accompanied by an injection of 10 mg ascorbic acid for approximately 25-27 days. In addition, 20 mg quercitrin was administered orally 5-6 hours following indole administrations for approximately 12 days. Urinary levels of excreted indoxysulfuric acid were reduced. Levels of free indole were not measured but were assumed to be less than 0.2 mg based on other experiments performed under similar conditions.

Reference No.: 308 (Sgibnev, A.K. and T.A. Orlova. Probl. Kosm. Biol. 1971)

Five rabbits were exposed to indole vapors at concentrations of 0.009-0.01 mg/l for 3 hours. Analysis of blood samples revealed no significant differences between test and control values in relation to plasma indole levels. The authors concluded that indole does not accumulate in the blood following inhalation of 0.009-0.01 mg/l.

Name of Substance: INDOLE [4]

Reference No.: 15 (Andrieu, L., et al. Eur. J. Med. Chem. Chim. Ther. 1974)

Species: Mouse (stock XVII & Merieux DFI)

Route: Intraperitoneal

No./Group: Not specified

Vehicle: Miglyol 812:triglyceride mixture

Duration: Acute

Control: Not specified

The intraperitoneal LD₅₀ for indole in mice was reported to be 300 mg/kg. No symptoms were noted.

Reference No.: 78a (Ehrhart, H. and W. Stich. Klin. Wochenschr. 1957)

Species: Mouse (RFH, white)

Route: Subcutaneous

No./Group: 50

Vehicle: Propylene glycol

Duration: 140 days

Control: Non-treated

Mice (an average of 18 g at onset of experiment) were given 0.5 mg indole subcutaneously at 3-4 day intervals resulting in an average of 1 mg/week over an approximate 140 day period with an observation period extending the experiment to a total of 360 days. No evidence of spontaneous leukemia was observed in control animals. Twenty percent mortality was noted within 4 weeks following a total dosage of 4 mg/mouse, and slight weight depression was observed. Hematology after 360 days showed a significant increase by an average of 5000 in total leukocytes over initial values. Leukemia with a high percentage of myeloblasts in peripheral blood was noted in 3 of 40 animals. Additional 31/40 mice exhibited no significant changes in differential blood count. Macro- and microscopic examination revealed leukemic infiltration of various organs (i.e., kidney and lungs), amyloidosis, and degenerative changes in the spleen, liver, and kidneys. Abnormal extramedullary blood formation centers were noted in the spleen and liver. The liver and spleen exhibited a high degree of myeloid metaplasia in the form of leukemic infiltrations.

In a parallel experiment, mice received total X-ray irradiation (i.e., 300 R or 6 x 50 R/1) prior to indole administration as above. Thirty percent mortality was noted in the initial 4 weeks. Hematology showed the presence of myeloblasts and myelocytes in differential blood counts. Bone marrow examinations showed an average of 15% immature myeloid type cells as opposed to 30% in controls. Histopathology revealed myeloid infiltration of various organs (kidney and lung), extramedullary blood centers exceeding normal values, and extreme enlargement of the spleen. The liver and spleen showed myeloid metaplasia as leukemic infiltrations. It was reported that a statistically significant difference existed between the leukemic rates of indole treated and control animals, and that X-ray pre-treatments produced no increases in leukemic frequency as opposed to indole treatments only. The authors concluded that indole possesses leukemogenic properties.

Name of Substance: INDOLE [4]

Reference No.: 86 (Felistovich, G.I. Vop. Onkol. 1964)

Species: Mouse (Afb)

No./Group: 16-170

Duration: 3 months

Route: Subcutaneous

Vehicle: Sunflower oil
with alcohol

Control: Vehicle alone

Mice, 2-3 months of age, were injected subcutaneously with a 10 mg/kg dose of indole once per week for 3 months. Of 170 control mice, 36% (61) died of leukemia, with 43 exhibiting the lymphoid type, 12 the myeloid type, and 6 showing hemocytoblastosis. In indole treatment, 13.5% (23/170) died of leukemia, with 14 displaying the lymphoid type, 6 the myeloid type, and 2 exhibiting hemocytoblastosis. During treatment 47/170 indole treated and 8/170 control mice died from additional causes. The authors concluded that indole protects animals of this strain from leukemia when administered at the specified age but enhances the incidence of death due to other causes.

Additional Afb mice, 7-8 months of age, were given subcutaneously 10 mg/kg of indole once per week for 3 months. Of 16 control animals, 4 developed leukemia spontaneously. In indole injected mice, 8 developed the myeloid form and death occurred between 67-75 days. One animal developed leukemia 25 days following treatment onset and death was observed 5 days later. An additional 3 mice developed peripheral lymphatic ganglions at 5 weeks and died soon after. The authors concluded that in Afb mice 7-8 months of age, indole increases the incidence of the development of leukemia.

Reference No.: 163 (Kader, M.M.A., et al. Jpn. J. Tuberc. 1960)

Species: Mouse (Swiss, white)

No./Group: 20

Duration: 15 days

Route: Subcutaneous

Vehicle: Propylene glycol

Control: Not specified

Mice were given a 25 mg/kg dose of indole subcutaneously once daily for 15 days. Pathological examination of animals sacrificed at 15 days and 8 weeks revealed no significant alterations in organs.

Name of Substance: INDOLE [4]

Reference No.: 308 (Sgibnev, A.K. and T.A. Orlova. Probl. Kosm. Biol. 1971)

Species: Mouse

No./Group: 20

Duration: 2 hours

Route: Inhalation

Vehicle: Air

Control: Not specified

Mice were subjected to the inhalation of indole vapors, diluted in normal atmosphere to concentrations of 0.009-0.01 mg/l, for a single 2-hour exposure period. Hyperactivity was observed during the initial 10-15 minutes following exposure after which time normal behavior was noted. No deaths occurred during the 14-day observation period.

Reference No.: 317 (Shinoda, M., et al. Yakugaku Zasshi. 1974)

Species: Mouse (DDY)

No./Group: 10 (M)

Duration: Acute

Route: Intraperitoneal

Vehicle: 5% Tween-80 in water

Control: Non-treated

The intraperitoneal LD₅₀ for indole in mice was reported to be 1-2 mmole/kg (ca 115-230 mg/kg).

Reference No.: 392 (Yanai, B. Tohoku. J. Exp. Med. 1935)

Species: Mouse

No./Group: Not specified

Duration: Acute

Route: Subcutaneous

Vehicle: Water or olive oil

Control: Not specified

The minimum lethal subcutaneous dose for indole in mice was reported to be 350-400 mg/kg. Toxic symptoms included an immediate crouching position, slowed and irregular breathing, staggering, and transient fascicular twitchings developing within 10 minutes of injection. Respiration increased but became more shallow. Twitchings developed into generalized clonic convulsions. Death occurred within 24 hours. Twitchings and convulsions, induced by indole, were eliminated in posterior sections of the body when the spinal cord was severed. Symptoms, though somewhat weakened, remained in the head region. The authors concluded that indole acts on motor elements of the spinal cord, and especially on the ganglion of the pons to increase their excitability and simultaneously lower reflex excitability.

Name of Substance: INDOLE [4]

Reference No.: 289 (Roe, D.A. J. Nutr. 1971)

Species: Rat (Sprague-Dawley)

No./Group: 6 (M)

Duration: 28 days

Route: Oral

Vehicle: Diet (8% casein)

Control: Diet alone

Indole was added to the diet (8% casein) of rats at levels of 0.125, 0.25, 0.5, 1.0 and 2.0% (equivalent to 62.5, 125, 250, 500 and 1000 mg/kg/day) for 28 days. No gross toxic effects were observed below a 0.25% dietary intake while significant reductions in hemoglobin content and hematocrit values were noted at 0.25%. At levels above 0.25%, food intakes and weight gains declined progressively. Dietary intakes of 1.0 and 2.0% produced coarse tremors, pallor of the ears, ataxia, frank anemia, and deaths in 1/6 and 3/6 animals, respectively, before completion of experiment. Analysis of pooled urine samples revealed increases in indican levels up to intakes of 0.25% indole, above which indican excretion levels remained constant. No changes in relative liver weights were noted at any level.

Reference No.: 308 (Sgibnev, A.K. and T.A. Orlova. Probl. Kosm. Biol. 1971)

Species: Rat

No./Group: 20

Duration: 2 hours

Route: Inhalation

Vehicle: Air

Control: Not specified

Rats were exposed for 2 hours to indole vapors diluted in normal atmosphere to concentrations of 0.009-0.01 mg/l. Hyperactivity was noted during the initial 10-15 minutes following exposure after which time normal behavior was noted. No deaths occurred during the 14-day observation period.

Reference No.: 324 (Smyth, H.F., Jr., et al. Am. Ind. Hyg. Assoc. J. 1962)

Species: Rat (Carworth-Wistar)

No./Group: 5 (M)

Duration: Acute (14 day observation)

Route: Oral (intubation)

Vehicle: Not specified

Control: Not specified

The oral range-finding LD₅₀ (Thompson-Weil) for indole in rats was reported to be 1.0 cc/kg (95% C.L. = 0.64-1.57 cc/kg) which is approximately equivalent to 1.22 g/kg (95% C.L. = 0.8-1.9 g/kg).

Name of Substance: INDOLE [4]

Reference No.: 163 (Kader, M.M.A., et al. Jpn. J. Tuberc. 1960)

Species: Human
No./Group: 3 (M)
Duration: 2-3 months

Route: Subcutaneous
Vehicle: Propylene glycol
Control: Not specified

Three male patients with tuberculosis for periods of 2 months to 5 years were given a 150 mg dose of indole subcutaneously once daily for up to 2-3 months. A 15-25% increase in weight was observed in addition to noted improvements in general condition. Symptoms of tuberculosis toxemia were alleviated and 70-90% reductions were observed in the amount of excreted sputum and in the number of mycobacterium bacilli present in the sputum. Measurements of urea clearance, alkaline phosphatase, and thymol turbidity were within normal limits, while levels of bilirubin were slightly higher than average values. One individual displayed jaundice and increases in thymol turbidity, alkaline phosphatase, and bilirubin 2 weeks after indole treatment. No changes in the X-ray picture in any of the 3 patients were observed.

Reference No.: 308 (Sgibnev, A.K. and T.A. Orlova. Probl. Kosm. Biol. 1971)

Species: Human
No./Group: 14
Duration: Single

Route: Inhalation
Vehicle: Air
Control: Not specified

Human volunteers received a single intranasal (i.e., whiff) exposure to indole vapors in concentrations equivalent to 0.12, 0.45, 0.9, 1.12, and 9.0 mg/m³. The threshold concentration for olfactory perception was reported to be 0.45 mg/m³. No significant effects on either respiration, electroencephalographic, or electrocardiographic measurements were noted. Occasional interference of respiratory reflexes and nausea were noted.

SAFETY DATA SHEET

GIVAUDAN

(from USDL Form LSB-00S-4)

SECTION 1 NAME & PRODUCT

MANUFACTURER'S NAME GIVAUDAN CORPORATION		EMERGENCY PHONE NO. (201) 546-8000	
ADDRESS 10 DELAWANNA AVENUE, CLIFTON, N. J. 07014		DATE THIS FORM WRITTEN October 10, 1979	
COMMON NAME AND SYNONYMS Indole		TRADE NAME Indole	
FAMILY PYRROLE		MOLECULAR FORMULA C_8H_7N	MOL. WT. 117.5

SECTION 2 INGREDIENTS

	%	TLV (units)

SECTION 3 PHYSICAL DATA

BOILING POINT (° C)	CA. 52°C	SPECIFIC GRAVITY @ 25° C (H ₂ O = 1)
MELTING POINT		% VOLATILE BY VOLUME
VAPOR PRESSURE (mmHg at 20° C)		COLOR White to off-white flake
DENSITY (air = 1)		ODOR Strong harsh odor
SOLUBILITY IN WATER		PHYSICAL STATE Solid

SECTION 4 FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (and method used) 200 °F TCC	FLAMMABLE LIMITS L.F.L.	U.F.L.
---	----------------------------	--------

☐ Water ☐ Fog ☐ Foam ☐ Alcohol ☐ Foam ☒ CO₂ ☒ Dry Chemical
☐ OTHER

ADDITIONAL FIRE AND EXPLOSION HAZARDS
NONE KNOWN

SECTION 5 REACTIVITY DATA

STABILITY	UNSTABLE	X	CONDITIONS TO AVOID Contact with iron or air may cause discoloration
	STABLE		
COMPATIBILITY with	☐ WATER ☐ ACID ☐ BASE ☐ CORROSIVE ☐ OXIDIZING MATERIAL		
	☐ OTHER		

HAZARDOUS DECOMPOSITION PRODUCTS
NONE KNOWN

HAZARDOUS POLYMERIZATION	MAY OCCUR	X	CONDITIONS TO AVOID
	WILL NOT OCCUR		

SECTION 6 HEALTH HAZARD DATA

LD LIMIT VALUE

OF OVER EXPOSURE (SKIN, EYE, INHALATION, ETC.)

Material is on the F.E.M.A. G.R.A.S. List. It is approved for food use
 .D.A. under 21 CFR 172.515 of the Food, Drug, and Cosmetic Act.
 al toxicity: LD₅₀ (rats) 1ml./kg. Maximization test: (1% solution)

no sensitization in humans.

PROCEDURES

ash with soap & water. Flush with copious quantities of water.

Flush with copious quantities of water. See physician.

on: Induce vomiting, see physician.

SECTION 7 SPILL OR LEAK PROCEDURES

BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED

Sweep up.

METHOD

ate in a suitable furnace or bury in an approved landfill.

Local State & Federal regulations.

SECTION 8 SPECIAL PROTECTION INFORMATION

LOCATION	LOCAL EXHAUST	SPECIAL
	XXX	
	MECHANICAL (General)	OTHER

FACTORY PROTECTION (SPECIFY TYPE)

Special

PROTECTIVE GLOVES

or synthetic

PROTECTIVE EQUIPMENT

EYE PROTECTION

Full goggles

SECTION 9 SPECIAL PRECAUTIONS OR OTHER COMMENTS

CTIONS TO BE TAKEN IN HANDLING AND STORING

Cosmetic, Toxicol, Volume 12 pp. 925-6 Pergamon Press, 1974

d in Great Britain.

PRECAUTIONS

FORMATION FURNISHED BY
 evy

TITLE
 Manager, Quality Assurance

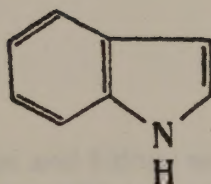
Information and recommendations contained in this Data Sheet are believed to be accurate and represent the best information
 available to us, but no warranty, guarantee or representation is made by Givaudan Corporation as to the absolute correctness
 of the information and recommendations in this Data Sheet; nor can it be assumed that all possible safety measures are
 indicated in this Data Sheet or that other or additional measures may not be required under varying conditions and circumstances.

OLE

C_8H_7N

French: *Indol*
German: *Indol*
Portuguese: *Indol*
Spanish: *Indol*

Mol. Wt. 117.15



benzopyrrole; 1-benzazole

Occurrence: Found in various oils of flowers such as jasmin, neroli, jonquil, wallflower, *Robinia pseudacacia* L., *Hedychium flavum* Roxb. and in oils of citrus.

Odor: Powerful and harsh odor, with a jasmin character on dilution.

Grades: Indole Pure and Indole Technical.

Color and Appearance: Indole Pure is a white crystalline material. The Technical grade is brownish.

Congealing Point: Minimum 51.0° (Pure).
Minimum 48.0° (Technical).

Method: Test V.

Stability and Discoloration: Moderately stable; causes discoloration.

Solubility: 1 gram is clearly soluble in 3 ml. of 70% alcohol.

Storage: Store in a cool place and protect from light. Use tightly-closed containers to avoid contaminating other materials.

Uses: This long-lasting product is used sparingly to give a floral effect, particularly in jasmin and lilac compositions, and in such other florals as honeysuckle, lotus, and orchid. Its power, strength, tenacity, will add desirable qualities when skillfully used in florals or in harmony with animal notes.

ISOBUTYL ALCOHOL

Isobutyl propanol

$(\text{CH}_3)_2\text{CHCH}_2\text{OH}$

50 ppm ($\approx 150 \text{ mg/m}^3$)

75 ppm ($\approx 225 \text{ mg/m}^3$)

Isobutyl alcohol is a colorless liquid with a molecular weight of 74.12 and a specific gravity of 0.806 at 15° C. It boils at 108.1° C, freezes at -108° C and has an open cup flash point of 100° F. The upper and lower explosive limits by volume in air are 10.9 and 1.2% at 212° F, respectively, and 9 mm Hg is the vapor pressure at 20° C. It is somewhat soluble in water, but miscible with most organic solvents.

It is used as a lacquer solvent, in paint removers, liquid chromatography, organic synthesis and esters for fruit flavoring essences.

Limited data^(1,2) on the acute experimental inhalation toxicity of isobutyl alcohol indicate it to be somewhat more toxic than n-butyl alcohol; a 4-hour LC_{50} exposure by inhalation for the rat was 8000 ppm vs greater than 8000 ppm for n-butyl alcohol. Isobutyl alcohol was slightly more acutely toxic to the rabbit orally (3.75 g/kg vs 4.25 g/kg for n-butyl alcohol). As the LD_{50} from skin application was 4.2 g/kg, no "Skin" designation is required for isobutyl alcohol, as this exceeds 2 g/kg, the suggested cut-off value for cutaneous "absorbable" substances.⁽³⁾ A narcotic dose for mice by inhalation for a total of 136 hours was reported by Weese⁽⁴⁾ to be 6,400 ppm; no deaths occurred from repeated narcotizing doses. Slight organic changes in the liv-

er and kidney were, however, found; whether they were reversible was not reported.

Although isobutyl alcohol is stated to be a skin irritant as evidenced by slight erythema and hyperemia upon application to human skin,^(5,6) no data are available on the effects of isobutyl alcohol vapor on the eyes. The injury to the eye caused by the liquid, however, is comparable to that from n-butanol.

As no reports of isobutyl alcohol causing either auditory impairment or vestibular damage have come to the attention of the Committee, the recommended TLV of 50 ppm and the STEL of 75 ppm must be based on its slightly greater acute toxic potential than n-butanol, whose former TLV of 100 ppm was based on its acute toxic response.

Other recommendations: Yugoslavia, 66 ppm; other countries, that have not yet adopted the 50 ppm TLV, retain, for the most part, the former TLV of 100 ppm.

References:

1. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S.: *Arch. Ind. Hyg. & Occup. Med.* 4:119 (1951).
2. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C.: *Ibid.* 10:61 (1954).
3. Stokinger, H.E.: Chapter II, *Occupational Exposure, Occupational Disease—Chemical, Physical and Biologic Agents—A Physicians Guide to Etiology*, US Government Printing Office, Washington, DC (1976).
4. Weese, H.: *Arch. Exptl. Path. Pharm.* 135:118 (1928).
5. Schwartz, L., Tulipan, L.: *A Textbook of Occupational Diseases of the Skin*, Lea & Febiger (1939).
6. Oettel, H.: *Arch. Exptl. Path. Pharm.* 183:641 (1936).

A-30

MATERIAL SAFETY DATA SHEET

(Approved by U.S. Department of Labor "Essentially Similar" to Form L5B-OOS-4)

ICAL NAME: ISOBUTANOL

NYMS: Isobutyl Alcohol; 2-Methyl-1-propanol;
Isopropylcarbinol

CHEMICAL FAMILY: Alcohols

RIULA: $\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$

MOLECULAR WEIGHT: 74.12

IE NAME AND SYNONYMS: Isobutanol; Isobutyl Alcohol

I. PHYSICAL DATA

ING POINT, 760 mm. Hg	107.9 °C. (226.2 °F.)	FREEZING POINT	-108 °C.
E FIC GRAVITY ($\text{H}_2\text{O} = 1$)	0.8030 at 20/20 °C.	VAPOR PRESSURE at 20 °C.	8 mm. Hg
PR DENSITY (air = 1)	2.55	SOLUBILITY IN WATER, % by wt. at 20 °C.	8.5
RENT VOLATILES OLUME	100	EVAPORATION RATE (Butyl Acetate = 1)	0.82
PARANCE AND ODOR	Water-white liquid; mild and nonresidual odor.		

II. HAZARDOUS INGREDIENTS

MATERIAL	%	TLV (Units)
Isobutyl Alcohol	~100	50 ppm.
(See Sections III through VIII)		

III. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (method)	82 °F., Tag closed cup	AUTOIGNITION TEMPERATURE	800 °F.	
FLAMMABLE LIMITS IN AIR, % by volume	LOWER	1.2	UPPER	10.9

EXTINGUISHING MEDIA	Use carbon dioxide or dry chemical for small fires. Use ordinary foam for large fires.
SPECIAL FIRE FIGHTING PROCEDURES	Water spray will decrease burning rate.
UNUSUAL FIRE AND EXPLOSION HAZARDS	None

EMERGENCY PHONE NUMBER

304/744-3487

This number is available days, nights, weekends, and holidays.

While Union Carbide Corporation believes that the data contained herein are factual and the opinions expressed are those of qualified experts regarding the results of the tests conducted, the data are not to be taken as a warranty or representation for which Union Carbide Corporation assumes legal responsibility. They are offered solely for your consideration, investigation, and verification. Any use of this data and information must be determined by the user to be in accordance with applicable federal, state and local laws and regulations.

IV. HEALTH HAZARD DATA

LIMIT VALUE	50 ppm. — ACGIH (1975 notice of intended changes) 100 ppm. — (OSHA) CFR 29 § 1000 Table G 1
OVEREXPOSURE	Contact with eyes is extremely irritating and may cause burns. Breathing vapors will be irritating to the nose and throat. In high concentrations, may cause nausea, dizziness, headache, and stupor.
SYMPTOMS AND FIRST AID PROCEDURES	Flush skin and eye contact at once with plenty of water. Get medical care for eyes. Remove inhalation exposure case to fresh air. Call a physician.

V. REACTIVITY DATA

STABILITY	CONDITIONS TO AVOID	Heat and flames.
STABLE		
✓		
STABILITY (to avoid)	None	
DECOMPOSITION PRODUCTS		Thermal decomposition or burning may produce carbon monoxide and/or carbon dioxide.
POLYMERIZATION	CONDITIONS TO AVOID	None
Will not Occur		
✓		

VI. SPILL OR LEAK PROCEDURES

TYPE OF SPILL OR LEAK	Small spills should be flushed with large quantities of water. Larger spills should be collected for disposal.
DISPOSAL METHOD	Incinerate in a furnace where permitted under appropriate Federal, State, and local regulations.

VII. SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (specify type)	Air-supplied respirator in confined areas.		
LOCAL EXHAUST	Preferable	SPECIAL	—
MECHANICAL (general)	Acceptable	OTHER	—
PROTECTIVE GLOVES	Plastic gloves	EYE PROTECTION	Coverall goggles
PROTECTIVE CLOTHING	Eye bath and safety shower		

VIII. SPECIAL PRECAUTIONS

ISOBUTANOL

DANGER! CAUSES EYE BURNS
HARMFUL IF INHALED
FLAMMABLE

Do not get in eyes.
Avoid breathing vapor.
Keep away from heat, sparks, and open flame.
Keep container closed.
Use with adequate ventilation.
Wash thoroughly after handling.

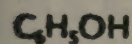
FIRST AID: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician.
If inhaled, remove to fresh air. If not breathing, give artificial respiration.
If breathing is difficult, give oxygen. Call a physician.

FOR INDUSTRY USE ONLY

CAUTIONARY LABELING

TER HANDLING AND
ORAGE CONDITIONS

PHENOL



Skin

TLV, 5 ppm ($\approx 19 \text{ mg/m}^3$)

STEL, 10 ppm ($\approx 38 \text{ mg/m}^3$)

Pure phenol is a solid at room temperature and is liquified by mixing with about 8% water. The molecular weight is 94.11 and the specific gravity is 1.071. It is white but often has a pinkish hue, resulting from impurities or exposure to light and has a characteristic sweet, tarry odor. The solid has a boiling point of 182°C and, when free from water and cresols, it congeals at 41°C and melts at 43°C . At 25°C it has a vapor pressure of 0.35 mm Hg. It is soluble in water and most organic solvents and is combustible, having a closed cup flash point of 172°F .

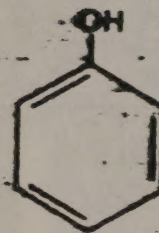
Its chief use is as a starting point in the manufacture of phenolic resins, bis-phenol-A, caprolactam and many other chemicals and drugs. It is employed as a disinfectant, in germicidal paints and as a slimicide.

Deichmann⁽¹⁾ reported results of animal experimentation in which guinea pigs were severely injured by inhalation for 20 days of phenol vapor at concentrations of from 25 to 50 ppm. Post mortem evidence of acute toxicity to the lungs, heart, liver and kidney was found.

Intermittent industrial exposure⁽²⁾ (five to ten minutes per hour) inside a conditioning room for phenol-impregnated asbestos resulted in marked irritation of the nose, throat and eyes. The average phenol concentration in the room was 48 ppm, although formaldehyde (8 ppm) also was found. Urine sulfate ratios were 79.4 and 86.7 percent. Workers at the same plant, continuously exposed during winding operations, experienced no respiratory irritation, although the odor of phenol was noticeable. The average concentration found was 4 ppm. Urine sulfate ratios averaged 74 percent.

Due in part to its low volatility, phenol does not frequently constitute a serious respiratory hazard in industry.⁽³⁾ Formerly its use as an antiseptic in surgery resulted in numerous cases of sub-acute or chronic poisoning among surgeons and their assistants.⁽⁴⁾ Urinary excretions of 2 grams per day, by patients, have been reported.⁽⁴⁾ Absorption of 2 grams of phenol could result from eight hours' inhalation at about 50 ppm.

According to Thomas and Back⁽⁵⁾ the TLV of 5 ppm provides a sufficiently large factor of safety to prevent systemic poisoning if skin absorption is avoided.



In 1976 NIOSH published a criteria document in which the toxicology of phenol was reviewed.⁽⁶⁾ The serious local and systemic effects of contact of the skin with phenol and its concentrated solutions were properly emphasized. Relatively little additional information on the effects of inhalation, bearing on the TLV, however, turned up. A report by Petrov⁽⁷⁾ of poisonings among workers in Russia, who quenched coke with waste water containing 0.3 to 0.8 mg of phenol per liter is discussed. Air samples indicated phenol vapor concentrations of the order of 2 to 3 ppm, and the author believed that phenol might have been implicated in the intoxications, which were not described.

The NIOSH recommendation of 20 mg/m^3 as a time-weighted average standard is essentially the same as the TLV of 5 ppm, established in 1952. The NIOSH ceiling of 60 mg/m^3 for any 15 minute period is higher than the STEL of 10 ppm (38 mg/m^3).

Except for the USSR, which has set an MAC of 1.3 ppm, most of the published hygienic standards (East and West Germany, Sweden, Czechoslovakia) are either 19 or 20 mg/m^3 , or, for practical purposes, 5 ppm.

References:

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2. Connecticut Bur. of Ind. Hygiene: Unpublished data.
3. Elkins, H.B.: *The Chemistry of Industrial Toxicology*, 2nd ed., p. 116, Wiley & Sons, NY (1959).
4. Patty, F.A.: *Industrial Hygiene & Toxicology*, 2nd ed., Vol. II, p. 1370, Interscience, NY (1963).
5. Thomas, A.A., Back, K.C.: *A Symposium on Toxicity in the Closed Ecologic System*, p. 135, Honma & Crosby Ed., Lockheed Missiles & Space Co., Palo Alto, CA (1964).
6. NIOSH: *Criteria for a Recommended Standard-Occupational Exposure to Phenol*, HEW Publication No. (NIOSH) 76-196 (1976).
7. Petrov, V.J.: *Cases of Phenol Vapor Poisoning During Coke Slaking with Phenol Water*, in Levine, B.S. (trans): *USSR Literature on Air Pollution and Related Occupational Diseases-A Survey*. U.S. Dept. of Commerce, National Technical Information Service 8:219 (1963) (NTIS 63-11570), Springfield, VA. Cited by NIOSH in ref. 6.

ia for a recommended standard

ational exposure to

HENOL

A-32
HEW Publication No. (NIOSH) 76-196

RTMENT OF HEALTH, EDUCATION, AND WELFARE

th Service Center for Disease Control

stitute for Occupational Safety and Health

National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 203
NTP No. 80-15
1980

**BIOASSAY OF
PHENOL
FOR POSSIBLE CARCINOGENICITY**

CAS No. 108-95-2

NCI-CG-TR-203

NTP-80-15

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health



SUMMARY

Phenol has been ranked 38th in production among U. S. chemicals with production of 2.38 billion pounds in 1978. A bioassay of phenol to test for possible carcinogenicity was conducted by providing this substance in drinking water to F344 rats and B6C3F1 mice. Groups of 50 rats and 50 mice of each sex were given drinking water containing 2,500 or 5,000 ppm phenol for 103 weeks. As matched controls, groups of 50 rats and 50 mice of each sex received tap water.

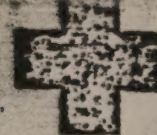
A dose-related depression in mean body weight gain occurred in rats and mice of each sex. Rats and mice given water containing phenol drank less than did the corresponding controls. A dose-related decrease in water consumption was observed for mice.

An increased incidence of leukemia or lymphomas was detected in male rats and may have been associated with the administration of phenol. Although the incidence of these tumors in the low-dose group was significantly higher than that in controls, the incidence in the high-dose group was not. Thus an association with administration of phenol was not established.

Under the conditions of this bioassay, phenol was not carcinogenic for either male or female F344 rats or male and female B6C3F1 mice.

MATERIAL SAFETY DATA SHEET

(Approved by U.S. Department of Labor "Essentially Similar" to Form LSH-005-4)



CHEMICAL NAME: PHENOL, USP

SYNONYMS: Carboic Acid; Hydroxybenzene

CHEMICAL FAMILY: Aryls

FORMULA: C_6H_5OH

MOLECULAR WEIGHT: 94.11

TRADE NAME AND SYNONYMS: Phenol

I. PHYSICAL DATA

BOILING POINT, 760 mm. Hg	181.8°C. (359.2°F.)	FREEZING POINT	40.9°C.
SPECIFIC GRAVITY ($H_2O = 1$)	1.0576 at 41/20°C.	VAPOR PRESSURE at 20°C.	< 0.1 mm.
VAPOR DENSITY (air = 1)	3.24	SOLUBILITY IN WATER, % by wt. at 20°C.	8.4
PER CENT VOLATILES BY VOLUME	100	EVAPORATION RATE (Butyl Acetate = 1)	< 0.01
APPEARANCE AND ODOR	White crystals; characteristic odor.		

II. HAZARDOUS INGREDIENTS

MATERIAL	%	TLV (Units)
Not applicable		

III. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (test method)	185°F., Cleveland open cup	AUTOIGNITION TEMPERATURE	1,319°F.
FLAMMABLE LIMITS IN AIR, % by volume	LOWER	1.7	UPPER 8.6
EXTINGUISHING MEDIA	Carbon dioxide or dry chemical for small fires. "Alcohol-type" foam for large fires.		
SPECIAL FIRE FIGHTING PROCEDURES	None		
UNUSUAL FIRE AND EXPLOSION HAZARDS	None		

IV. HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE	5 ppm. Skin
SIGNS OF OVEREXPOSURE	Causes skin and eye burns. May penetrate skin, rapidly causing collapse and sudden death. Breathing vapors will cause irritation and may cause nausea and vomiting.
SYMPTOMS AND FIRST AID PROCEDURES	Remove to fresh air if inhaled. Flush eye contact at once with plenty of water for at least 15 minutes. Get medical care. For skin contact, immediately flush with water while scrubbing contact area of skin. Remove clothing and wash underlying skin. Get medical care at once.

V. REACTIVITY DATA

STABILITY		CONDITIONS TO AVOID	None
BLE	STABLE		
	✓		
ATIBILITY (to avoid)		Contamination with alkalis.	
OUS POSITION PRODUCTS		Thermal decomposition may produce carbon monoxide and/or carbon dioxide.	
OUS POLYMERIZATION		CONDITIONS TO AVOID	None
cur	Will not Occur		
	✓		

VI. SPILL OR LEAK PROCEDURES

PRECAUTIONS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED	Isolate the area. Cover with sand or dirt and/or allow to solidify. Shovel into a metal container for disposal. Flush the area thoroughly with water. Wash contaminated equipment thoroughly. Avoid contamination of water way.
DISPOSAL METHOD	1. Incinerate with adequate supervision. 2. Bury in a landfill.

VII. SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (specify type)		Fresh air mask for confined areas	
METHOD OF PROTECTION	LOCAL EXHAUST	Preferable	SPECIAL
	MECHANICAL (general)	Acceptable	OTHER
PROTECTIVE GLOVES	Rubber gloves	EYE PROTECTION	Full face shield
ADDITIONAL PROTECTIVE MEASURES	Protective clothing, eye bath, and safety shower		

VIII. SPECIAL PRECAUTIONS

CAUTIONARY LABELING



PHENOL, USP



DANGER!

RAPIDLY ABSORBED THROUGH SKIN.
ABSORPTION THROUGH SKIN
HARMFUL OR FATAL.
CAUSES SEVERE BURNS.

Do not get on skin, in eyes, or on clothing.
Avoid breathing vapor.
Use with adequate ventilation.
Do not take internally.



POISON



In case of contact:

CLOTHING — Remove contaminated clothing and shoes at once. Wash thoroughly before reuse.

SKIN — Immediately flush with plenty of water for at least 15 minutes. Get medical attention.

EYES — Immediately flush with plenty of water for at least 15 minutes. Get medical attention.

FOR INDUSTRY USE ONLY

ER HANDLING AND
RAGE CONDITIONS

PHENOL

**DANGER! MAY BE FATAL IF SWALLOWED
HARMFUL IF INHALED OR ABSORBED THROUGH SKIN**

Avoid breathing vapor.
Avoid contact with eyes, skin, and clothing.
Keep container closed.
Use with adequate ventilation.
Wash thoroughly after handling.



POISON



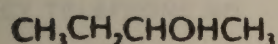
Call a Physician

FIRST AID: If swallowed, induce vomiting by sticking finger down throat or by giving soapy or strong salty water to drink. Repeat until vomit is clear. Never give anything by mouth to an unconscious person.

If inhaled, remove to fresh air. If not breathing give artificial respiration, preferably mouth-to-mouth. If breathing is difficult, give oxygen.

In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before re-use. (Discard contaminated shoes.)

sec-BUTYL ALCOHOL



TLV, 100 ppm ($\approx 305 \text{ mg/m}^3$)

STEL, 150 ppm ($\approx 455 \text{ mg/m}^3$)

sec-Butyl alcohol is a colorless liquid with a strong vinous odor. Its molecular weight is 74.12, specific gravity is 0.808 at 20° C and the vapor pressure is 13 mm Hg at the same temperature. The boiling point is 99.5° C, with a freezing point of -114° C. It has a closed cup flash point of 75° F and an autoignition temperature of 763° F, making it a dangerous fire risk. It is moderately soluble in water and miscible with most organic solvents.

It is used in the synthesis of flotation agents, flavors, perfumes, dyestuffs and wetting agents. Also in industrial paint removers and cleaners.

Limited data on the acute toxicity of sec-butyl alcohol indicate it to be less harmful than n-butanol. Smyth *et al.*^(1,2) found the oral LD₅₀ values for rats to be 6.5 and 4.4 g/kg, respectively. Five or six rats exposed at 16,000 ppm of sec-butyl alcohol vapor for four hours died. This was more than twice the maximal concentration attainable with n-butanol⁽³⁾ that caused no deaths in eight hours.

The TLV for n-butanol, however, is based partly on its effects on the eyes. No information is available on eye irritation from sec-butyl alcohol vapor. In liquid form it was less injurious to the eyes than n-butanol.

This relatively meager information suggests that the TLV should be as high, or higher, than that of n-butyl alcohol. There is one report that many years of industrial experience with exposures approximating 100 ppm "have resulted in no difficulties".⁽⁴⁾

A TLV of 100 ppm, twice that of its normal isomer, is recommended for sec-butyl alcohol to prevent narcotic and irritative effects. A STEL of 150 ppm is also suggested.

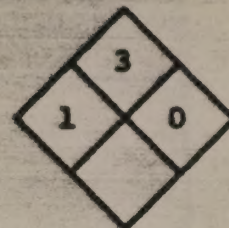
Other recommendations: West Germany (1976) 100 ppm; Sweden (1974) 50 ppm.

References:

1. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S.: *Arch. Ind. Hyg. & Occup. Med.* 4:119 (1951).
2. Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C.: *Ibid.* 10:61 (1954).
3. Mellan, L.: *Industrial Solvents*, 2nd ed., p. 489, Reinhold Pub. Corp., NY (1950).
4. Bank, O.M.: Communication to TLV Committee (February 1966).

MATERIAL HEALTH AND SAFETY BULLETIN

Union Chemicals Division
Petrochemical Group



No.: 827

Product Code No.: 5350

UN No. -

MANUFACTURER'S NAME

Union Chemicals Division, Union Oil Company of California

STREET ADDRESS

~~1345 North Meacham Road~~ *1900 E. Gulf Rd.*

CITY, STATE, AND ZIP CODE

Schaumburg, Illinois 60196

Business Phone: (312) 885-5450

EMERGENCY TELEPHONE NO.

Transportation Emergencies call CHEMTREC (800) 424-9300

Health Emergencies Call Los Angeles Poison Control Center (24 hours) (213) 664-2121

PRODUCT: **sec-Butanol**
COMMON NAME: **AMSCO Solv 5350**
GENERIC NAME: **Volatile Solvent**
CHEMICAL NAME: **Secondary Butanol**
CHEMICAL FAMILY: **Oxygenated Hydrocarbon**
PROPER SHIPPING NAME:
Alcohol NOS

WARNING STATEMENT:

Warning Flammable.
Induce vomiting if swallowed.
For industrial use only.

Section I - - INGREDIENTS

	TLV*		TLV*
sec-Butanol	150		

Threshold Limit Value

A, OSHA ☒

B, ACGIH ☐

C. See Section III ☐

D, Other ☐

Section II - - EMERGENCY AND FIRST AID PROCEDURES

CY: Have a physician call LOS ANGELES POISON CONTROL CENTER (24 hrs.) 213/664-2121

If this product comes in contact with the eyes, flush with large quantities of water for at least 15 minutes and seek immediate medical attention.

If this product comes in contact with the skin, wash with large quantities of water and seek medical attention if irritation from contact persists.

If breathing difficulties, dizziness, or lightheadedness occur when working in areas with high vapor concentrations, victim should seek air free of vapors. If victim experiences continued breathing difficulties, administer oxygen until medical assistance can be rendered. If breathing stops, begin artificial respiration and seek immediate medical attention.

If this product is swallowed, induce vomiting if the victim is conscious. Seek immediate medical advice and/or attention.

Section III - - PHYSIOLOGICAL EFFECTS AND HEALTH INFORMATION

This product may be an eye irritant.

This product may cause skin irritation upon prolonged or repeated contact. Contact with this product may result in dermatitis upon prolonged or repeated contact.

Various studies have shown a possible association with exposure to this product and the following:

Respiratory tract irritation

Central nervous system depression in high concentrations

Nausea and vomiting

Section IV - - SPECIAL PROTECTION INFORMATION

The use of respiratory protection depends on vapor concentration above the time-weighted TLV; use a NIOSH approved cartridge respirator or gas mask.

General mechanical ventilation may be sufficient to keep product vapor concentrations within specified time-weighted TLV ranges. If general ventilation proves inadequate to maintain safe vapor concentrations, supplemental local exhaust may be required. Other special precautions such as respiratory masks or environmental containment devices may be required in extreme cases.

The use of impermeable gloves is advised to prevent skin irritation in sensitive individuals.

Eye Protection

Safety glasses, chemical goggles and/or face shields are recommended to safeguard against potential eye contact, irritation, or injury.

Impermeable aprons are advised when working with this product. The availability of eye washes and safety showers in work areas is recommended.

Section V - - REACTIVITY DATA

Unstable

Stable

X

Conditions to Avoid:

This product is incompatible with strong oxidizing agents, strong acids or bases, alkali metals and halogens.

Thermal decomposition in the presence of air may yield carbon monoxide and/or carbondioxide.

May Occur

Will Not Occur

X

Conditions to Avoid:

Section VI - - SPILL OR LEAK PROCEDURES

HIGHWAY OR RAILWAY SPILLS - CALL CHEMTREC 800/424-9300

Keep sources of ignition and hot metal surfaces isolated from the spill. Flush spilled material into suitable retaining areas or containers with large quantities of water. Small amounts of spilled material may be absorbed into an appropriate absorbant.

Notify Coast Guard National Response Center; Phone No. 800-424-8802, If Spill Is Greater Than lbs (Kilograms)

Dispose of product in accordance with applicable local, county, state and federal regulations.

Section VII - - STORAGE AND SPECIAL PRECAUTIONS

Keep product containers cool, dry, and away from sources of ignition. Use and store this product with adequate ventilation. (See Section IV.) Keep product containers closed when not in use.

Personnel should avoid inhalation of vapors. (See sections I, II, III, V, VI) Personal contact with the product should be avoided. Should contact be made, remove saturated clothing and flush affected areas with water. (See sections II, IV, VI)

Section VIII - - FIRE AND EXPLOSION HAZARD DATA

Flammable Liquid

Flash Point Range: ☐ Below 20° F, ☒ 20° F - 100° F
☐ 100° F - 200° F ☐ Over 200° F
☐ None to boiling

Use foam, CO₂ or dry chemical fire fighting apparatus.

Keep work areas free of hot metal surfaces and other sources of ignition.

The use of self-contained breathing apparatus is recommended for fire fighters. Water may be unsuitable as an extinguishing media, but helpful in keeping adjacent containers cool. Avoid spreading burning liquid with water used for cooling purposes.

Section IX - - PHYSICAL DATA

Approximate Boiling Range, ° F

211° F.

Vapor Density: ☒ Heavier Than Air
☐ Lighter

Evaporation Rate: ☐ Faster Than Ether
☒ Slower

Percent Volatile: 100%

Solubility in Water: 20%

Specific Gravity: ☒ Lighter Than Water
☐ Heavier

Weight per Gallon: 6.72

Appearance and Odor: This product is clear, has little if any color and has a characteristic odor.

Section X - - DOCUMENTARY INFORMATION

Product Code No. 5350 Issue Date 10/22/80 Prepared By Paul Pfeifer

UCD No. Product Code No. Issued

Reviewed By: *G. Jettin* Manager, Loss Prevention

Reviewed By: *Rainer Beck* Director of Occupational Health & Toxicology

Reviewed By: *Fulankh...* Science and Technology Division

The above information is believed to be correct as of the date hereof. However, no warranty of merchantability, fitness for any use, or any other warranty is expressed or is to be implied regarding the accuracy of these data, the results to be obtained from the use of the material, or the hazards connected with such use. Since the information contained herein may be applied under conditions beyond our control and with which we may be unfamiliar, and since data made available subsequent to the date hereof may necessitate modification of the information, we do not assume responsibility for the results of its use. This information is furnished on the condition that the person receiving it shall make his own determination as to the suitability of the material for his particular purpose and on the condition that he assume the risk of his use thereof.

The Aliphatic Acids and Their Esters: Toxicity and Potential Dangers

The Saturated Monobasic Acids and Their Esters:

Aliphatic Acids with Three to Eighteen Carbons and Their Esters

W. F. von OETTINGEN, M.D., Ph.D., Bethesda, Md.

Propionic Acid

Chemistry.—Propionic acid, propanoic acid, $\text{CH}_3\text{CH}_2\text{COOH}$, has the molecular weight 74.08. It is a colorless liquid of pungent odor; has the specific gravity 0.993 at 20/4 C, the melting point -20.8°C , and boiling point 141.4°C . It is miscible with water, alcohol, and ether, and, in contrast to the lower homologues, it may be salted out from its aqueous solutions by means of calcium chloride and other readily water-soluble salts. With ferric salts and arsenic trioxide it gives the same reactions as acetic acid, and its lead salt is less soluble in hot than in cold water (Rosenthaler, 1923).

Uses.—Propionic acid is used as esterifying agent, in the manufacture of cellulose propionate, of ester solvents, fruit flavors, and perfume bases, and as fungistatic agent.

Antiseptic Properties.—As shown by Bach (1932) propionic acid has moderate antiseptic properties, and it is in this respect somewhat more effective than acetic acid. Peck and Rosenfeld (1938) showed that it has fungistatic properties down to concentrations of 0.004 mol per liter, and that it is in this respect somewhat superior to acetic acid but inferior to the higher homologues with straight carbon chains. Miller (1939) studied the retarding effect of its sodium and calcium salts on molds in dairy products; and Keeney (1943) found that 1.25% solutions adjusted to pH 5.5 had fungistatic properties for *Trychophyllum purpureum*, *Epidermophyton inguinale*, *Microsporum audouinii*, *Candida albicans*, *Aspergillus fumigatus*, and *Aspergillus flavus*, that one-tenth this concentration (0.125%) prevented the growth of *Trychophyllum gypsum*, *Trychophyllum violaceum*, *Epidermophyton rubrum*, *Epidermophyton interdigitale*, *Trychophyllum schoenleinii*, and *Microsporum lanosum*, and that 0.0125% solutions prevented the growth of *Blastomyces dermatitidis*.

Received for publication June 15, 1959.

National Institute of Arthritis and Metabolic Diseases; National Institutes of Health; Department of Health, Education, and Welfare; U.S. Public Health Service, Bethesda, Md.

Clinical studies on the efficacy against various fungus infections were published by Keeney and Broyles (1943).

Irritant Action.—Propionic acid causes moderate irritation of the human skin. As shown by Oettel (1936), its contact with the human skin for 40 minutes caused distinct burning pain, erythema, and hyperemia, but less marked than that observed with acetic acid. This was followed by moderate erythema and pigmentation, and very moderate necroses.

Absorption, Fate and Excretion.—Propionic acid is readily absorbed from the gastrointestinal tract. There is no evidence that it is absorbed through the intact human skin, and in view of its high boiling point its absorption through the lungs appears quite remote. As shown by Blum (1910), and MacKay, Wick and Barnum (1940), it is not oxidized with the formation of ketone bodies by rabbits with adequate amounts of glycogen in the liver. As shown by Ringer (1912), and Rittenberg, Schoenheimer and Evans (1937), it is largely converted to glucose in phlorizinized animals, and according to Buchanan, Hastings and Nesbett (1943) it is partly converted to glycogen in fasted rats, in contrast to acetic acid. It appears to be not excreted as such in the urine, because, as shown by Hermann and associates (1938), it is decomposed in the intestine by bacterial destruction.

Toxicity for Laboratory Animals.—Propionic acid is comparatively little toxic. According to Mayer (1886) the intravenous injection of 2.2 gm. per kilogram, given as 14% solution, causes in rabbits marked

against various
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TABLE 1.—Physical-Chemical Properties of Alkyl Propionates *

Name	Methyl Propionate	Ethyl Propionate	Propyl Propionate	n-Butyl Propionate	i-Amyl Propionate
Formula	$\text{CH}_3\text{CH}_2\text{COOCH}_3$	$\text{C}_2\text{H}_5\text{CH}_2\text{COOC}_2\text{H}_5$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{COOC}_2\text{H}_5$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COOC}_2\text{H}_5$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOC}_2\text{H}_5$
Molecular weight	88.10	102.13	116.16	130.18	144.21
Specific gravity	0.915 20/4 C	0.890 18/4 C	0.883 20/4 C	0.883 15 C	0.870 20/4 C
Boiling point, C	79.7	90.1	122.0	146	160.2
Flash point, F (C) (closed cup)	28 (-2.22)	54 (12.22)	—	80 (32.20)	—
Solubility in water	0.5/100 20 C	2.4/100 20 C	0.66/100 25 C	insoluble	0.1/100 25 C
in alcohol	miscible	miscible	miscible	miscible	miscible
in ether	miscible	miscible	miscible	—	—
40 mm. Vapor press. at C	11.0	27.2	45.0	—	—
100 mm. Vapor press. at C	29.0	45.2	65.2	—	—
Solvent for: †		Cellulose nitr. Colophony Ester gum Chlorine rubber Gum ester Oil and Fats	Cellulose nitr. Colophony Celluloid Chlorine rubber	Cellulose nitr. Copal ester Benzylacetate Mastic Ester gum Dammar Coumarone Elemi Celluloid Chlorine rubber Cellulose acet. Hard copals Sandarac Zanzibar Glycerolphthalate	Cellulose nitr. Celluloid Chlorine rubber Colophony Copal ester Resins Ester gum Benzylacetate Coumarone Elemi Cellulose acet. Shellac Dammar Hard copal
Does not dissolve: †		Cellulose acet.			

* Lange, 1908.

† Durrans (1944), Gnamn (1943).

dyspnea, increased cardiac action, pareses, and frequent urination, followed by recovery within 24 hours. Similar effects, although less severe, were seen in dogs after intravenous injection of 0.55 gm/kg. (given as 10% solution), and in cats after subcutaneous injection of 1 gm/kg., given as 10% solution. As shown by Fodera (1894) the injection of 2 cc. of a 5% neutralized solution of propionic acid, corresponding to 0.1 gm., causes in frogs fibrillary twitchings and pareses, lasting about 24 hours. As reported by Hermann (1930) the intravenous injection of 0.37 gm. (given as N/2 solution) causes in dogs a distinct, although temporary, fall of the blood pressure.

Toxicity for Man.—There are no reports on toxic effects of propionic acid in man, and dangers and hazards from this material appear quite remote.

Aliphatic Esters of Propionic Acid

Table 1 gives a synopsis of the physical-chemical properties of the five lowest aliphatic esters of propionic acid. It shows that their specific gravity and solubility in water decrease with their molecular weight, and that their boiling points and flash points move in the opposite direction.

It also gives a partial list of the compounds for which these esters are used as solvents, and it illustrates their extensive use. In spite of this, none of these compounds have been studied toxicologically in detail.

Treon and associates (1949) determined the minimal lethal dose for methyl propionate with oral administration to rabbits as 2.55 to 3.2 gm/kg., and found that such doses cause ataxia, prostration, labored, gasping respiration, and marked hyperthermia. For ethyl propionate they gave the minimal lethal oral dose as 3.2 to 3.95 gm/kg., the symptoms being the same as reported with the lower homologue. As shown by Vogel (1897) the oral administration of 0.6 and 1.0 cc/kg. causes in rabbits stimulation of the respiratory volume. According to Fühner and Neubauer

(1907) the in vitro hemolytic action of the propionic acid esters increases with the molecular weight from methyl over ethyl to propyl propionate, the minimum effective concentrations being 0.34, 0.17, and 0.06 mol per liter, respectively.

There are no reports on the toxic effects of these esters for man, and, in view of their relatively high vapor pressure, toxic effects from the inhalation of their vapors seem to be quite remote.

An ether-ester of propionic acid which has been studied toxicologically is ethyl- β -ethoxy propionate, ethoxypropionic acid ethyl ester, $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$, which has the molecular weight 146, specific gravity 0.948 at 25/25 C, and boils at 165-172 C (Scheffan and Jacobs, 1953). According to Smyth, Carpenter and Weil (1954) it is very little toxic, the oral LD_{50} for rats being 5.0 gm/kg., and that with cutaneous application to rabbits about 10 cc/kg. Its contact with the skin causes a minimum degree of irritation, and when instilled into the eye it causes some irritation.

Butyric Acid

Chemistry.—Butyric acid, butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$, is a colorless liquid of the molecular weight 88.10 and the specific gravity 0.958 at 20/4 C, which melts at -5.5 C, boils at 164.1 C, and which is miscible with water, alcohol, and ether. Its flash point is 170 F (76.67 C) (closed cup method). It may be salted out from its aqueous solutions by means of calcium chloride. The sodium salt differs from that of propionic acid by its great solubility in amyl alcohol. When heated with sulfuric acid and methanol, or with potassium ethyl sulfate, a pineapple-like odor is formed (Rosenthaler, 1923).

Antiseptic Properties.—As shown by Bach (1932) butyric acid has antiseptic properties which are more marked than those of propionic acid. Similarly, Peck and Rosenfeld (1938) found that its fungistatic action for *Trychophyton gypseum* is greater than that of the lower homologues, the minimum concentration being 0.00113 mol per liter (0.01%), as compared with 0.00405 mol per liter and 0.00498 mol per liter for propionic acid and acetic acid, respectively.

Irritant Action.—The irritant action of butyric acid is less marked than that of propionic acid. According to Oettel (1936)

the application to the intact human skin is followed only after 52 minutes by very moderate burning, and erythema and hyperemia are hardly noticeable; this is followed within 24 hours by slight scaling of the epidermis.

Absorption, Fate and Excretion.—Butyric acid is absorbed from the gastrointestinal tract, but other routes of absorption have apparently not been studied. As to its fate in the metabolism, Marx (1910) found that its oral administration to fasted dogs results occasionally and its intraperitoneal injection regularly in the excretion of acetoacetic acid, and that this ketogenic action is less marked in animals fed carbohydrates. Blum (1910) showed that in dogs the subcutaneous injection of butyric acid results in the excretion of β -hydroxybutyric acid, acetoacetic acid, and acetone; the β -hydroxybutyric acid being presumably formed secondarily from acetoacetic acid. Ehrmann (1913) found acetoacetic acid and acetone in the urine of rabbits after oral administration of butyric acid. Bloch and Rittenberg (1944) showed that, after oral administration to rats, a considerable portion of butyric acid is metabolized to acetic acid. Experiments of Rittenberg, Schoenheimer and Evans (1937) indicate that this oxidation takes place rapidly. It evidently takes place in the liver, as indicated by perfusion experiments with this organ by Embden, Salomon, and Schmidt (1906), and Embden and Engel (1908), and the experiments with liver slices and liver juice as reported by Leloir and Munoz (1939). From the reports of Ciaranfi (1938) and Kleinzeller (1943) it appears, however, that similar oxidative processes may also take place in the kidneys. Experiments reported by Buchanan, Hastings and Nesbett (1943) with rats show that oral administration of butyric acid will increase the glycogen content of the liver.

Toxicity of Butyric Acid for Animals.—Butyric acid causes a depression of the central nervous system, as demonstrated in frogs by Fodera (1894) and Sternberg

(1898). According to the latter, doses of 0.1 gm. cause only clumsy movements, doses of 0.3 gm. prolonged depression, and doses of 0.5 gm. profound depression, followed by death after several days. Similarly Mayer (1886) reported that in rabbits the intravenous administration of 1.6 gm/kg. of sodium butyrate causes a marked temporary depression of the central nervous system. According to the same author the intravenous injection of 0.86 gm/kg. of sodium butyrate, given as 30% solution, causes in dogs vomiting, staggering, and deep sleep lasting one hour. Similar effects were produced in cats after subcutaneous doses of 0.5 gm/kg. (given as 10% solution). Marx (1910) and Ehrmann (1911, 1913) pointed to the similarity between diabetic coma and the toxicological picture produced by the intravenous injection of butyric acid.

Ehrmann and Esser (1911) found that the oral administration of small doses of sodium butyrate does not materially affect the circulation, whereas, as shown by Ehrmann (1913), large intravenous doses impair the cardiac action and cause a fall of the blood pressure, presumably on account of formation of β -hydroxybutyric acid and acetoacetic acid. Loewy and Ehrmann (1911) noted in rabbits a decrease of the carbon dioxide content of the blood during coma produced by the oral administration of 3.3 to 3.6 gm/kg. of sodium butyrate, which presumably was also produced by the formation of keto bodies. Fühner and Neubauer (1907) studied the in vitro hemolytic action of butyric acid, the minimum effective concentration being 0.0081 mol per liter.

According to Ehrmann (1911) the fatal dose of butyric acid with oral administration for rabbits is 3.6 to 3.7 gm/kg., and according to Dreyfus (1920) the toxicity for the same species is greatest with rectal administration, less marked with subcutaneous injection, and least with oral administration.

There are no reports on toxic effects of butyric acid for man.

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TABLE 2.—Physical-Chemical Properties of Alkyl Butyrates *

Name	Methyl Butyrate	Ethyl Butyrate	Propyl Butyrate	Butyl Butyrate	Amyl Butyrate
Formula	$C_5H_{10}O_2$	$C_7H_{14}O_2$	$C_9H_{18}O_2$	$C_{11}H_{22}O_2$	$C_{13}H_{26}O_2$
Molecular weight	102.13	116.16	130.18	144.21	158.23
Specific gravity	0.903 16/4 C	0.874 25/4 C	0.879 16 C	0.872 20/20 C	0.871 16/4 C
Freezing point, C	-84.8	-100.8	-95.2	—	-73.2
Boiling point, C	102.8	121.6	142.7	165.7 730 mm.	186.4
Flash point, F (C)	87 (13.80)	78 (25.50)	—	—	—
Solubility in water	1.7/100	0.68/100 25 C	0.17/100 17 C	Insoluble	0.05/100 50 C
in alcohol	miscible	miscible	miscible	miscible	miscible
in ether	miscible	miscible	miscible	miscible	miscible
Solvent for: †		Cellulose nitr. Chlorine rubber Ester gum Coumarone Mastic Colophony Manilla Gutta percha resin Ethyl cellulose Cellulose acetate Glyceryl phthalate Rosin	Cellulose nitr. Chlorine rubber Celluloid Some resins	Cellulose nitr. Ester gum Coumarone Mastic Dammar Eloint Shellac Zinc resinate Cellulose acetate Sandarac Zantibar Hard copal	Cellulose nitr. Chlorine rubber Celluloid Some resins

* Lange, 1950.

† Durrans (1944), Gramm (1943).

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TOXICITY OF SOME ALIPHATIC ACIDS AND ESTERS

Aliphatic Esters of Butyric Acid

As illustrated in Table 2, the specific gravity and solubility in water of the aliphatic esters of butyric acid decrease with the molecular weight, whereas boiling point and flash point move in the opposite direction.

There are only very few reports on the toxicological properties of these compounds. Fühner and Neubauer (1907) studied the hemolytic properties of the two lowest members of this series in vitro, and determined the minimum effective concentration of methylbutyrate as 0.14 mol per liter, and that of ethyl butyrate as 0.06 mol per liter.

According to Albertoni and Lussana (1874) the ethyl ester causes, in doses of 3 gm. (given in 60 cc. of water), no toxic effects in dogs. Similarly, the intravenous injection of 177 mg/kg. into the femoral vein, and of 222 mg/kg. into the jugular vein caused no toxic effects. Doses of 300 mg. given orally to one rooster and one pigeon had neither local nor systemic effects, whereas larger doses caused marked irritation. According to Vogel (1897) doses of 2.14 cc/kg. in rabbits cause an increase of the respiratory volume.

Smyth, Seaton, and Fischer (1941) studied the toxicity of another butyric acid ester, triethyleneglycol diethyl butyrate, also called "Flexol" plasticizer 3GH, triglycol-dicaprate, or triglycol-dihexoate, $C_5H_{11}COOCH_2(CH_2OCH_2)CH_2COOC_5H_{11}$, which according to Scheflan and Jacobs (1953) has the molecular weight 346.5, the specific gravity 0.9946 at 20/20 C, a boiling point of 358.0 C at 760 mm. Hg and a flashpoint of 385 F (196.11 C) (open cup method), and which is soluble in water to the extent of 0.02 parts per 100 at 20 C. They found it very little toxic, the oral LD_{50} for rats being 8.42 gm/kg., and that for guinea pigs 3.13 gm/kg.

Smyth, Carpenter and Weil (1951) studied the toxicity of vinyl butyrate $C_4H_7CH_2COOCH=CH_2$, and found that its oral toxicity for rats is 8.530 gm/kg., that air saturated with its vapors may be inhaled by rats for 30 minutes without death, and

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that exposure for four hours to a concentration of 4000 p.p.m. was fatal to three out of six animals. There was no evidence of irritation of the skin or of the eyes.

In spite of the paucity of information on the toxicity of butyric acid esters, it appears that these are of a low order of toxicity.

Isobutyric Acid

Isobutyric acid, methylpropanoic acid, $(CH_3)_2CHCOOH$, is a colorless liquid of molecular weight 88.10, specific gravity 0.949 at 20/4 C, freezing point -47 C, which boils at 154.7 C, is soluble in water to the extent of 20 parts per 100 at 20 C, and miscible with alcohol and ether. It differs from butyric acid in that it is less soluble in water, and that its salts are generally more water-soluble than those of butyric acid.

Peck and Rosenfeld (1938) determined the minimum fungicidal concentration for *Trychophyton gypseum* as 0.00795 mol per liter, as compared with 0.00113 mol per liter found for butyric acid. Very little is known on the pharmacological and toxicological properties of this compound. According to Embden, Salomon and Schmidt (1906) it differs from butyric acid in that it does not form acetone in the perfused liver. As shown by Loewy and Ehrmann (1911) doses of 5 to 6.1 gm/kg. of sodium isobutyrate cause in rabbits no coma but a decrease of the carbon dioxide content of the blood. Ehrmann (1911) determined the oral fatal dose for rabbits as 8 gm/kg.; isobutyric acid being, therefore, less toxic than butyric acid, for which the corresponding value was found to be 3.6 to 3.7 gm/kg. body weight.

There are no reports on the toxicity of isobutyric acid for man.

Valeric Acid

Valeric acid, pentanoic acid, $CH_3CH_2CH_2CH_2COOH$, has the molecular weight 102.13. It is a colorless liquid of unpleasant odor and the specific gravity 0.940 20/4 C, which melts at -34.5 C and boils at 186.4 C. It is soluble in water to the extent of 3.3 parts per 100 at 16 C, and it is miscible with

less neutral liquid of peculiar, not unpleasant odor, of the molecular weight 158.23 and specific gravity 0.862 at 25/4 C, which boils at 168.8 C, and which has the flash point 127.4 F (53 C). According to Gnamm (1943) it is used as solvent for cellulose acetate and celluloid.

Its toxicity has evidently not been studied, nor has it given rise to toxic effects in man.

Methyl-Ethyl-Acetic Acid

Another isomer of valeric acid is methyl-ethyl-acetic acid, methyl-butyric acid, $C_2H_5-CH_2CHCOOH$, which is a colorless liquid of unpleasant odor, the molecular weight 102.13, and the specific gravity 0.938 at 20/20 C, which boils at 174-177 C, and is slightly soluble in water but miscible with alcohol and ether. According to Seidell (1919) the solubility of its calcium salt in water of 20 C is 25.23 gm. per 100.

According to Peck and Rosenfeld (1938) the minimum fungistatic concentration of the acid for *Trychophyton gypsum* is the same as for valeric and isovaleric acid, namely 0.00293 mol per liter.

According to Lang and Adickes (1940) it is less readily oxidized by liver tissue than isobutyric acid.

Trimethyl-Acetic Acid

Trimethyl-acetic acid or pivalic acid ($(CH_3)_3CCOOH$) is another isomer of valeric acid. It forms colorless needles of the specific gravity 0.905 at 50 C which melt at 35.5 C and boil at 163.8 C. It is soluble in water of 20 C to the extent of 2.1 gm. per 100, and it is very soluble in alcohol and ether. According to Seidell (1919) the solubility of its calcium salt in water of 20 C is only 6.14 gm. per 100.

According to Dziewiatkowski and Lewis (1945) single oral doses of 25 to 250 mg. per 100 grams of body weight, given as sodium salt, cause no toxic effects in young white rats, nor were these observed when doses of 25 to 100 mg. per 100 grams were administered daily for periods from 7 to 14 days. Similarly, the salt was found relatively

nontoxic for rabbits. The ingestion was followed by a considerable increase of the urinary glucuronic acid, indicating that it is not completely oxidized in the organism, but partly excreted as glucuronide.

Caproic Acid

Caproic acid, hexanoic acid, $CH_3(CH_2)_4COOH$, is an oily liquid of unpleasant odor, the molecular weight 116.16, and the specific gravity 0.931 at 15/4 C, which melts at -4 C and boils at 205.4 C. It is soluble in water to the extent of 1.10 parts per 100 at 20 C, and it is soluble in alcohol and ether. Its calcium salt is soluble in water up to 2.18 gm. per 100 at 20 C (Seidell, 1919).

According to Peck and Rosenfeld (1938) it has marked fungicidal properties, the minimum effective concentration of *Trychophyton gypsum* being 0.00077 mol per liter.

Experiments reported by Rittenberg, Schoenheimer, and Evans (1937) indicate that, like butyric acid, caproic acid is rapidly oxidized in the organism; that it is not stored, nor converted to higher fatty acids, and that for this reason it is not a fat-former in the accepted sense. Leloir and Munoz (1939) assumed that caproic acid is oxidized by β -oxidation, and studies by Morehouse and Deuel (1940) indicate that δ -oxidation also plays an important part in the oxidative metabolism of caproic acid.

Smyth and Carpenter (1944) estimated the minimal fatal dose for rats with single oral administration as 3 gm/kg. of body weight, and that for guinea pigs with cutaneous application at 5.0 gm/kg. They found that it causes marked irritation of the skin and of the eyes. Hall and Waldman (1946) found that the intravenous injection of 3 cc. of sodium caproate per kilogram, given as 0.25 molar solution in a 25% solution of human albumin (103.62 mg/kg.), caused disturbances of the cardiac rhythm characterized by multiple ventricular ectopic systoles, various types of coupled beats, and idioventricular rhythm.

Alkylesters of Caproic Acid

The alkylesters of caproic acid are evidently not used industrially. The octylester occurs in the fruits of *Gingho biloba*, but it has evidently not been studied toxicologically, except that, according to Oettel (1936), its application for five hours to the intact human skin causes no signs of irritation.

According to Deuel, Hallman, Butts, and Murray (1936) the administration of ethylcaproate to fasting rats gives rise to ketonuria which is somewhat less marked than that produced by sodium caproate.

Isocaproic Acid

Isocaproic acid, 2-methylpentanoic-5-acid, $(\text{CH}_3)\text{CH}(\text{CH}_2)_2\text{COOH}$, has the molecular weight 116.16, and is a colorless liquid of the specific gravity 0.923 at 20/4 C, which melts at -33°C and boils at 199.5°C . It is very slightly soluble in water but soluble in alcohol and ether.

Embden, Salomon and Schmidt (1906) found no evidence of acetone formation when this acid was perfused through livers, but Lang and Adickes (1940) found that digestion with liver tissue does yield acetone, presumably because of demethylation and β -oxidation.

There are no reports on the toxicity of this acid for animals or man.

Diethylacetic Acid

Diethylacetic acid, $(\text{C}_2\text{H}_5)_2\text{CHCOOH}$, another isomer of caproic acid, has the molecular weight 116.16, and is a colorless liquid of the specific gravity 0.920 at 18/0 C, which melts at -15°C , boils at 195°C , and which is slightly soluble in water and soluble in alcohol and ether.

Embden and Wirth (1910) found that perfusion of the liver with this acid yields some ketonic compounds, presumably acetoacetic acid and 1- β -hydroxybutyric acid. Blum and Koppel (1911) found that feeding the acid in doses of 11.6 gm. to dogs fasted for 24 hours resulted in the excretion of methyl-propyl-ketone with the urine, and

they assumed that this is formed by β -oxidation.

There are no reports on the toxicity of this material for animals or man.

Heptanoic Acid

Heptanoic acid, heptioic acid, oenanthylic acid, $\text{CH}_3(\text{CH}_2)_5\text{COOH}$, has the molecular weight 130.18. It is a colorless liquid of the specific gravity 0.922 at 15/4 C, which melts at -7.5°C , boils at 223.0°C , and is soluble in water to the extent of 0.25 parts per 100 at 15°C , and soluble in alcohol and ether. It is one of the constituents of fusel oil.

Peck and Rosenfeld (1938) determined the minimum fungistatic concentration of heptanoic acid for *Trychophyton gypseum* as 0.00053 mol per liter.

According to MacKay, Wick, and Barnum (1940) the administration of heptanoic acid to rabbits gives rise to keto-bodies in the blood, and, as pointed out by Leloir and Munoz (1939), it appears to undergo β -oxidation in the organism. Hall and Waldman (1946) noted that the intravenous injection of 114.12 mg/kg., given as 0.25% molar solution in 25% human albumin solution, causes in cats anesthetized with sodium pentobarbital disturbances of the cardiac rhythm, such as multiple ventricular ectopic systoles, various types of coupled beats, and idioventricular rhythm.

Aliphatic Esters of Heptanoic Acid

The only aliphatic ester of heptanoic acid of interest is the ethyl ester, ethyl heptanoic acid, ethyl oenanthate, $\text{CH}_3(\text{CH}_2)_5\text{COOC}_2\text{H}_5$. It has the molecular weight 158.23, and is a colorless liquid of pleasant odor of the specific gravity 0.872 at 20/20 C, which melts at -66.1°C , boils at $187-188^\circ\text{C}$, and which is soluble in water of 20 C to the extent of 0.029 parts per 100, and miscible with alcohol, chloroform, and ether.

According to Oettel (1936) contact for five hours with the human skin causes no irritation, and according to Vogel (1897) oral doses of 1.88 cc/kg. cause in rabbits a slight increase in respiratory volume.

Caprylic Acid

Caprylic acid, octanoic acid, $\text{CH}_3(\text{CH}_2)_6\text{COOH}$, has the molecular weight 144.21, and is a colorless liquid of the specific gravity 0.908 at 20/4 C, which melts at -33.9°C , boils at 239.3°C , and which is soluble in water to the extent of 0.25 parts per 100 at 100°C to the extent of 0.25 parts per 100 at 100°C and soluble in alcohol, chloroform, and ether. It is soluble in water to the extent of 0.25 parts per 100 at 40°C (Se

Peck and Rosenfeld (1938) determined the minimum fungistatic concentration of caprylic acid for *Trychophyton gypseum* as 0.00028 mol per liter.

Leloir and Munoz (1939) found that caprylic acid is oxidized in the liver with liver slices, yielding ketonic acids. According to Adickes (1940), the administration of caprylic acid results in the formation of acetone, and Floyd (1944) found that acetic acid thus formed reacts down with the formation of ketone. It appears that only a small amount of caprylic acid can be acetylated. The oxidation of ketone to carbon dioxide is that part of the acid which is the active reaction leading to tissue.

Hall and Waldman (1946) performed experiments with pentobarbital and the intravenous injection of sodium caprylate, a 0.25% molar solution in a 25% human albumin, causes disturbances of the cardiac rhythm, characterized by multiple ventricular systoles, various types of coupled beats, and idioventricular rhythm, which could be antagonized by the administration of potassium salts. According to Elliott, Kipple and Waldman (1946) further that concentration of 0.025 mol, in glucose

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TOXICITY OF SOME ALIPHATIC ACIDS AND ESTERS

Its toxicity for animals or man has apparently not been studied.

Caprylic Acid

Caprylic acid, octanoic acid, $\text{CH}_3(\text{CH}_2)_6\text{COOH}$, has the molecular weight 144.21. It forms colorless leaflets of the specific gravity 0.908 at 20/4 C, which melt at 16.3 C, boil at 239.3 C, and which are soluble in water of 100 C to the extent of 0.25 parts per 100, and soluble in alcohol, carbon disulfide, chloroform, and ether. Its calcium salt is soluble in water to the extent of 0.28 gm. per 100 at 40 C (Seidell, 1919).

Peck and Rosenfeld (1938) determined the minimum fungistatic concentration of caprylic acid for *Trychophyton gypsum* as 0.0028 mol per liter.

Leloir and Munoz (1939) showed that caprylic acid is oxidized when incubated with liver slices, with the formation of ketonic acids. According to Lang and Adickes (1940), this results also in the formation of acetone. Weinhouse, Medes, and Floyd (1944) showed that the acetoacetic acid thus formed is further broken down with the formation of acetone, but it appears that only a small fraction of caprylic acid can be accounted for by the formation of ketone bodies or by complete oxidation to carbon dioxide, and it appears that part of the acid undergoes a nonoxidative reaction leading to its fixation in the tissue.

Hall and Waldman (1946) showed, in experiments with pentobarbitalized cats, that the intravenous injection of 124.65 mg/kg. of sodium caprylate, given as 5 cc. of a 0.25 molar solution in a 25% solution of human albumin, causes disturbances of the cardiac rhythm, characterized by multiple ectopic ventricular systoles, various types of coupled beats, and idioventricular rhythm, which could be antagonized by the administration of potassium salts. Perfusion experiments with the isolated frog heart reported by Elliott, Kipple and Hall (1947) showed further that concentrations between 0.000625 to 0.025 mol, in glucose-Ringer solution, in-

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crease the cardiac output under conditions of constant venous pressure and peripheral resistance, and that this effect is brought about by an increase in stroke volume, apparently because of an improvement of the contractility of the muscle.

Esters of Caprylic Acid

Ethyl caprylate, $\text{CH}_3(\text{CH}_2)_6\text{COOC}_2\text{H}_5$, has the molecular weight 172.26 and is a colorless liquid of the specific gravity 0.871 at 15/4 C, which melts at -43.2 C and boils at 208.5 C, and which is insoluble in water but soluble in alcohol and ether.

According to Deuel, Hallman, Butts, and Murray (1936) its administration to fasting rats results in a more marked ketonuria than observed with the methyl esters of capric, lauric, and myristic acid.

The vinyl ester of 2-ethylhexanoic acid, *vinyl-2-hexanoate*, was studied by Smyth and associates (1954), who determined its oral LD_{50} for rats as 4,290 mg/kg., and found that rats may tolerate without fatalities exposure for eight hours to a saturated vapor-air mixture, and that the mixture causes some irritation of the skin and the eye.

The *triethylene glycol caprylate*, "Plasticizer SC" (Drew) is, according to Mallette and von Haam (1952), practically nontoxic, rats tolerating the intraperitoneal injection of 6 gm/kg. or more. Its topical application causes in rabbits moderate irritation of the skin but no evidence of sensitization.

The corresponding ester of 2-ethylhexanoic acid, *triethylene glycol di-(2-ethylhexanoate)*, is even less toxic, inasmuch as the oral LD_{50} for rats and guinea pigs is 31.37 and 20.58 gm/kg., respectively, as determined by Smyth and associates (1941).

The glyceryl ester of caprylic acid, *tricaprylin*, glyceryltricaprylate, $(\text{C}_7\text{H}_{15}\text{COO})_3\text{C}_3\text{H}_8$, has the molecular weight 470.67, and is a colorless liquid of the specific gravity 0.954 at 20/4 C which melts at 8.3 C, and is insoluble in water but soluble in 85% alcohol and ether.

effects, the triglyceride was studied by Verkade and coworkers (1933, 1934) who found that its ingestion results in the formation of little or no keto-bodies, and results in no increased excretion of lactic acid but in a considerable excretion of diacidoic acid. MacKay, Wick, and Barnum (1940) found that feeding of the ethyl ester to rabbits gives rise to the presence of ketone bodies in the blood, as was the case with the esters of valeric, heptylic, and pelargonic acid.

Lauric Acid

Lauric acid, dodecanoic acid, $\text{CH}_3(\text{CH}_2)_{10}\text{COOH}$, has the molecular weight 200.31, and forms colorless needles of the specific gravity 0.871 at 50/4 C which melt at 44.1 C, boil at 255 C at 100 mm. Hg., and are insoluble in water, but soluble in alcohol, benzene, ether, and petroleum ether. It occurs as glyceride in many fats, and its alkali salts may be salted out by sodium chloride but less readily than with the higher aliphatic acids.

Whereas the free acid has evidently not been studied biologically, feeding of the triglyceride, trilaurin, to rats resulted in the formation of fat deposits containing as much as 25% of lauric acid (Powell, 1930), and Verkade and van der Lee (1934) found that it has practically no diacidogenic action. According to Kesten, Salcedo and Stetten (1945) feeding of ethyl laurate at a level of 35-40% to young rats receiving no choline resulted in death from heart failure in three to six days, the animals suffering from a diffuse interstitial myocarditis, which could be prevented by feeding adequate amounts of choline, betaine, or methionine. Quantities of up to 25% could be fed without fatalities. According to Deuel and associates (1936) administration of ethyl laurate to fasting rats results in distinct ketonuria.

Tridecylic Acid

Tridecylic acid, tridecanoic acid, $\text{CH}_3(\text{CH}_2)_{11}\text{COOH}$, has the molecular weight 214.34 and forms colorless crystals which melt at 41 C, boil at 199-200 C at 24 mm.

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Hg, and are insoluble in water but very soluble in alcohol and ether.

Whereas the free acid has apparently not been studied biologically, the triglyceride, tridecylin, has according to Verkade and van der Lee (1934) no diacidogenic action.

Myristic Acid

Myristic acid, tetradecanoic acid, $\text{CH}_3(\text{CH}_2)_{12}\text{COOH}$, has the molecular weight 228.36, and forms colorless leaflets of the specific gravity of 0.853 at 70/4 C which melt at 54.2 C, boil at 250.5 C at 100 mm. Hg, are insoluble in water, but are very soluble in absolute alcohol, benzene, and ether. It occurs as glyceride in many fats, especially in those of nutmeg, coconut, and butter. According to Deuel and associates (1936) the ethyl ester of myristic acid causes ketonuria when fed to fasting rats.

Palmitic Acid

Palmitic acid, hexadecanoic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{COOH}$, has the molecular weight 256.42, and forms colorless platelets of the specific gravity 0.849 at 70/4 C which melt at 62.8 C, boil at 271.5 C at 100 mm. Hg, and are insoluble in water, very slightly soluble in petroleum ether, soluble in alcohol, and freely soluble in chloroform and ether. The glyceride of palmitic acid is a constituent of many fats, the cetyl ester occurring in sperm oil, and the myricyl ester in beeswax.

There are no reports on the physiological action of palmitic acid except an observation of Guggenheim and Löffler (1918) that the sodium salt causes depression of the isolated intestine in concentrations of 0.01 to 0.1 gm/100 cc.

Swern and associates (1943) synthesized 1-ascorbylpalmitate in *d*-isoascorbyl palmitate, which were proposed by Riemen-schneider and co-workers (1944) as antioxidants for fats and oils. However, Fitzhugh and Nelson (1946) showed that feeding these compounds to rats in concentrations of 5% in the diet caused retardation of growth, and, in two animals, bladder

stones. Chronic feeding experiments extending over a period of two years indicated that both compounds are nontoxic in a concentration of 0.25% (2,500 p.p.m.) or less of the total diet of rats.

Stearic Acid

Stearic acid, octadecanoic acid, $\text{CH}_3(\text{CH}_2)_{16}\text{COOH}$, has the molecular weight 284.47, and forms monoclinic crystals of the specific gravity 0.847 at 69.5 C which melt at 69.6 C, boil at 291 C at 110 mm. Hg, are soluble in water to the extent of 0.03 parts per 100 at 25 C, slightly soluble in alcohol (2% at 20 C), more soluble in ether (6% at 15 C), and soluble in acetone and benzene. It is a constituent of most fats.

As shown by Dakin (1908) the ammonium salt of stearic acid is oxidized by hydrogen peroxide in the presence of a trace of ferrous sulfate, at least in part, to β -ketones. Some of the biological properties of this acid are mentioned in the comparison of physical-chemical and toxicological properties of saturated aliphatic acids.

As reported by Cronin (1925) contact of the skin with molten stearic acid may cause an itchy dermatitis with dryness of the skin, fissures, and desquamation.

As shown by Stetten and Salcedo (1945) feeding of *ethyl stearate* at a level of 35% in the diet to young male rats, receiving no choline, causes marked fatty changes in the liver.

Butyl stearate, which is used as a plasticizer, as shown by Smith (1953), is tolerated by rats without lethal effects in doses as large as 32 gm/kg. without gross pathologic changes, except increased respiration which became evident five minutes after the administration and lasted one or two days. Chronic feeding experiments extending over a period of two years showed that feeding concentrations of 1.25 and 6.25% in the diet affected neither the growth nor the survival adversely; that it did not produce significant hematological changes in the peripheral blood, nor of the cellular dis-

tribution, or of the myeloid-erythroid ratio of the bone marrow. At the 6.25% level, butyl stearate had no effect on the fertility or the number of viable young rats in the litter, but it retarded slightly their growth.

Department of Health, Education and Welfare,
U.S. Public Health Service.

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MATERIAL SAFETY DATA SHEET

(Approved by U.S. Department of Labor "Essentially Similar" to Form LSB-OOS-4)

PRODUCT NAME: VALERIC ACID

COMMON NAME: --

CHEMICAL FAMILY: Acids

FORMULA: C_4H_9COOH

MOLECULAR WEIGHT: 102.13

SYNOPSIS: Valerianic Acid; n-Pentanoic Acid

I. PHYSICAL DATA

BOILING POINT, 760 mm. Hg	185.5 °C. (365.9 °F.)	FREEZING POINT	-34 °C.
SPECIFIC GRAVITY (H ₂ O = 1)	0.9406 at 20/20 °C.	VAPOR PRESSURE AT 20°C.	< 0.1 mm. Hg
DENSITY (air = 1)	3.5	SOLUBILITY IN WATER, % by wt.	2.4
PERCENT VOLATILES BY VOLUME	100	EVAPORATION RATE (Butyl Acetate = 1)	0.015
APPEARANCE AND ODOR	Water-white liquid; unpleasant odor.		

II. HAZARDOUS INGREDIENTS

MATERIAL	%	TLV (Units)
Valeric Acid	~ 100	Not established
(See Sections III through VIII)		

III. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (Method(s))	205 °F., Cleveland open cup ASTM D 92 193 °F., Tag closed cup ASTM D 56			
FLAMMABLE LIMITS IN AIR, % by volume	LOWER	2.7	UPPER	7.6
EXTINGUISHING	Use carbon dioxide or dry chemical for small fires. Use foam (alcohol, polymer, or ordinary) for large fires.			
SPECIAL FIRE FIGHTING PROCEDURES	Self-contained breathing apparatus should be available to firemen.			
ADDITIONAL FIRE AND EXPLOSION HAZARDS	None			

EMERGENCY PHONE NUMBER

304/744-3487

This number is available days, nights, weekends, and holidays.

While Union Carbide Corporation believes that the data contained herein are factual and the opinions expressed are those of qualified experts regarding the results of the tests conducted, the data are not to be taken as a warranty or representation for which Union Carbide Corporation assumes legal responsibility. They are offered solely for your consideration. Investigation, and verification. Any use of these data and information must be determined by the user to be in accordance with applicable Federal, State, and local laws and regulations.

UNION CARBIDE CORPORATION • CHEMICALS AND PLASTICS • 270 PARK AVENUE, NEW YORK, N.Y. 10017

IV. HEALTH HAZARD DATA

OLD LIMIT VALUE	None established by ACGIH or OSHA
OF OVEREXPOSURE	Vapors will cause coughing and irritation of nose and throat. Contact with the liquid causes burns both of skin and eyes.
Y AND FIRST EDURES	If inhaled, remove to fresh air. If breathing is difficult, give oxygen and call a physician. In case of contact with skin or eyes, immediately flush with plenty of water for at least 15 minutes. Get medical care for eyes.

V. REACTIVITY DATA

STABILITY		CONDITIONS TO AVOID	None
BLE	STABLE		
-	✓		
TIBILITY (to avoid)		Avoid strong alkalies.	
US SITION PRODUCTS		Burning can produce carbon monoxide and/or carbon dioxide.	
US POLYMERIZATION		CONDITIONS TO AVOID	None
Occur	Will not Occur		
-	✓		

VI. SPILL OR LEAK PROCEDURES

BE TAKEN AL IS RELEASED D	Wear suitable protective equipment. Collect for disposal. Toxic to fish; avoid discharge to natural waters.
POSAL METHOD	Incinerate in a furnace where permitted under appropriate Federal, State, and local regulations.

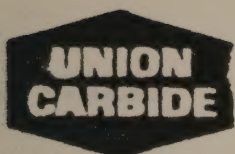
VII. SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (specify type)		Air-supplied mask for high concentrations		
VENTILATION	LOCAL EXHAUST	Preferred - See Section VIII	SPECIAL	--
	MECHANICAL (general)	✓	OTHER	--
PROTECTIVE GLOVES		Plastic or rubber	EYE PROTECTION	Monogoggles
OTHER PROTECTIVE EQUIPMENT		Safety shower, eye bath, and coveralls		

VIII. SPECIAL PRECAUTIONS

CAUTIONARY LABELING	VALERIC ACID DANGER! CAUSES BURNS COMBUSTIBLE Do not get in eyes, on skin, on clothing. Keep away from heat and open flame. Avoid breathing vapor. Keep container closed. Use with adequate ventilation. Wash thoroughly after handling. FIRST AID: In case of contact, immediately flush eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Call a physician. Wash clothing before reuse. FOR INDUSTRY USE ONLY
	Valeric acid has a very disagreeable odor that is detectable at very low concentrations in air (about 0.001 ppm.). The acid should be confined within equipment and special ventilation provided at locations where release is likely to occur. This acid is highly toxic to fish; it should not be allowed to enter natural waterways. It may be feasible to treat dilute solutions (200 ppm. or less) in a wastewater treatment facility or to neutralize the acid and treat the sodium salt.

OTHER HANDLING AND STORAGE CONDITIONS



UNION CARBIDE CORPORATION OLD RIDGEBURY ROAD, DANBURY, CT 06817
Solvents and Intermediates Division

Enclosed is the Material Safety Data Sheet you

requested recently. Should you have any questions, please feel free to contact the Union Carbide Sales Office nearest you.

**Material Safety Data Department
SOLVENTS & INTERMEDIATES DIVISION**

HEAT STRESS

These Threshold Limit Values (TLVs) refer to heat stress conditions under which it is believed that nearly all workers may be repeatedly exposed without adverse health effects. The TLVs shown in Table 1 are based on the assumption that nearly all acclimatized, fully clothed workers with adequate water and salt intake should be able to function effectively under the given working conditions without exceeding a deep body temperature of 38° C (WHO technical report series #412, 1969 *Health Factors Involved in Working Under Conditions of Heat Stress*; F.N. Dukes-Dobos and A. Henschel: "Development of Permissible Heat Exposure Limits for Occupational Work." ASHRAE Journal, Vol. 15: No. 9, September 1973, pp. 57-62).

Since measurement of deep body temperature is impractical for monitoring the workers' heat load, the measurement of environmental factors is required which most nearly correlate with deep body temperature and other physiological responses to heat. At the present time Wet Bulb Globe Temperature Index (WBGT) is the simplest and most suitable technique to measure the environmental factors. WBGT values are calculated by the following equations:

1. Outdoors with solar load:

$$WBGT = 0.7WB + 0.2GT + 0.1 DB$$
2. Indoors or Outdoors with no solar load:

$$WBGT = 0.7WB + 0.3GT$$

where:

WBGT = Wet Bulb Globe Temperature Index
 WB = Natural Wet-Bulb Temperature
 DB = Dry-Bulb Temperature
 GT = Globe Thermometer Temperature

The determination of WBGT requires the use of a black globe thermometer, a natural (static) wet-bulb thermometer, and a dry-bulb thermometer.

Higher heat exposures than shown in Table 1 are permissible if the workers have been undergoing medical surveillance and it has been established that they are more tolerant to work in heat than the average worker. Workers should not be permitted to continue their work when their deep body temperature exceeds 38.0° C.

TABLE 1

Permissible Heat Exposure Threshold Limit Values
 (Values are given in °C WBGT)

Work — Rest Regimen	Work Load		
	Light	Moderate	Heavy
Continuous work	30.0	26.7	25.0
75% Work — 25% Rest, Each hour	30.6	28.0	25.9
50% Work — 50% Rest, Each hour	31.4	29.4	27.9
25% Work — 75% Rest, Each hour	32.2	31.1	30.0

Evaluation and Control

I. Measurement of the Environment

The instruments required are a dry-bulb, a natural wet-bulb, a globe thermometer, and a stand. The measurement of the environmental factors shall be performed as follows:

- A. The range of the dry and the natural wet-bulb thermometers shall be -5° C to 50° C with an accuracy of ±0.5° C. The dry-bulb thermometer must be shielded from the sun and the other radiant surfaces of the environment without restricting the airflow around the bulb. The wick of the natural wet-bulb thermometer shall be kept wet with distilled water for at least 1/2 hour before the temperature reading is made. It is not enough to immerse the other end of the wick into a reservoir of distilled water and wait until the whole wick becomes wet by capillarity. The wick shall be wetted by direct application of water from a syringe 1/2 hour before each reading. The wick shall extend over the bulb of the thermometer, covering the stem about one additional bulb length. The wick should always be clean and new wicks should be washed before using.
- B. A globe thermometer, consisting of a 15 cm (6-inch) diameter hollow copper sphere painted on the outside with a matte black finish or equivalent, shall be used. The bulb or sensor of a thermometer (range -5° C to 100° C with an accuracy of ±0.5° C) must be fixed in the center of the sphere. The globe thermometer shall be exposed at least 25 minutes before it is read.
- C. A stand shall be used to suspend the three thermometers so that they do not restrict free air flow around the bulbs, and the wet-bulb and globe thermometer are not shaded.
- D. It is permissible to use any other type of temperature sensor that gives identical reading as that of a mercury thermometer under the same conditions.
- E. The thermometers must be so placed that the readings are representative of the condition where the men work or rest, respectively.

The methodology outlined above is more fully explained in the following publications:

1. Minard, D.: *Prevention of Heat Casualties in Marine Corps Recruits, Period of 1955-1960, with Comparative Incidence Rates and Climatic Heat Stresses in Other Training Categories*, Research Report No. 4, Contract No. MR 005.01-0001.01, Naval Medical Research Institute, Bethesda, MD (February 21, 1961). Published in *Military Medicine* 126(4):261-272 (April 1961).
2. Minard, D. and R.L. O'Brien: *Heat Casualties in the Navy and Marine Corps 1959-1962 with Appendices on the Field Use of the Wet Bulb-Globe Temperature Index*, Research Report No. 7, Contract No. MR 005.01-0001.01, Naval Medical Research Institute, Bethesda, MD (March 12, 1964).

II. Work Load Categories

Heat produced by the body and the environmental heat together determine the total heat load. Therefore, if work is to be performed under hot environmental conditions, the work load category of each job shall be established and the heat exposure limit pertinent to the work load evaluated against the applicable standard in order to protect the worker from exposure beyond the permissible limit.

A. The work load category may be established by ranking each job into light, medium, and heavy categories on the basis of type of operation. Where the work load is ranked into one of said three categories, i.e.,

- (1) light work (up to 200 kcal/hr or 800 Btu/hr), e.g., sitting or standing to control machines, performing light hand or arm work,
- (2) moderate work (200-350 kcal/hr or 800-1400 Btu/hr), e.g., walking about with moderate lifting and pushing,
- (3) heavy work (350-500 kcal/hr or 1400-2000 Btu/hr), e.g., pick and shovel work.

The permissible heat exposure limit for that work load shall be determined from Table 1.

B. The ranking of the job may be performed either by measuring the worker's metabolic rate while performing his job or by estimating his metabolic rate by the

use of the scheme shown in Table 2. Tables available in the literature listed below and in other publications as well may also be utilized. When this method is used, the permissible heat exposure limit can be determined by Figure 1.

References:

1. Astrand, Per-Olof and Kaare Rodahl: *Textbook of Work Physiology*, McGraw-Hill Book Co., New York, San Francisco (1970).
2. Ergonomics Guide to Assessment of Metabolic and Cardiac Costs of Physical Work, *Am. Ind. Hyg. Assoc. J.* 32:560 (1971).
3. Purdue University: *Energy Requirements for Physical Work*, Research Progress Report No. 30, Purdue Farm Cardiac Project, Agricultural Experiment Station (1961).
4. Dumin, J.V.G.A. and R. Passmore: *Energy, Work and Leisure*, Heinemann Educational Books, Ltd., London (1967).

TABLE 2

Assessment of Work Load

Average values of metabolic rate during different activities.

A. Body position and movement		kcal/min	
Sitting		0.3	
Standing		0.6	
Walking		2.0-3.0	
Walking up hill		add 0.8 per meter (yard) rise	
B. Type of Work		Average kcal/min	Range kcal/min
Hand work			
	light	0.4	0.2-1.2
	heavy	0.9	
Work with one arm			
	light	1.0	0.7-2.5
	heavy	1.8	
Work with both arms			
	light	1.5	1.0-3.5
	heavy	2.5	
Work with body			
	light	3.5	2.5-15.0
	moderate	5.0	
	heavy	7.0	
	very heavy	9.0	

Light hand work: writing, hand knitting	
Heavy hand work: typewriting	
Heavy work with one arm: hammering in nails (shoemaker, upholsterer)	
Light work with two arms: filing metal, planing wood, raking of a garden	
Moderate work with the body: cleaning a floor, beating a carpet.	
Heavy work with the body: railroad track laying, digging, barking trees	
Sample Calculation: Using a heavy hand tool on an assembly line	
A.	Walking along 2.0 kcal/min
B.	Intermediate value between heavy work with two arms and light work with the body 3.0 kcal/min
	Sub-Total 5.0 kcal/min
C.	Add for basal metabolism 1.0 kcal/min
	Total 6.0 kcal/min

Adapted from Lehmann, G.E., A. Muller and H. Spitzer: *Der Kalorienbedarf bei gewerblicher Arbeit. Arbeitsphysiol.* 14:166 (1950).

III. Work-Rest Regimen

The permissible exposure limits specified in Table 1 and Figure 1 are based on the assumption that the WBGT value of the resting place is the same or very close to that of the work place. Where the WBGT of the work area is different from that of the rest area, a time-weighted average value should be used, for both environmental and metabolic heat. When time-weighted average values are used the appropriate curve on Figure 1 is the solid line labeled "continuous."

The time-weighted average metabolic rate (M) shall be determined by the equation:

$$Av. M = \frac{(M_1) \times (t_1) + (M_2) \times (t_2) + \dots + (M_n) \times (t_n)}{(t_1) + (t_2) + \dots + (t_n)}$$

Where M_1, M_2, M_n are estimated or measured metabolic rates for the various activities of the worker during the total time period. t_1, t_2, t_n are the elapsed times in minutes spent at the corresponding metabolic rate as determined by a time study.

The time-weighted average WBGT shall be determined by the equation:

$$Av. WBGT = \frac{(WBGT_1) \times (t_1) + (WBGT_2) \times t_2 + \dots + (WBGT_n) \times (t_n)}{(t_1) + (t_2) + \dots + (t_n)}$$

Where $WBGT_1, WBGT_2, WBGT_n$ are calculated values of WBGT for the various work and rest areas occupied during total time periods. t_1, t_2, t_n are the elapsed times in minutes

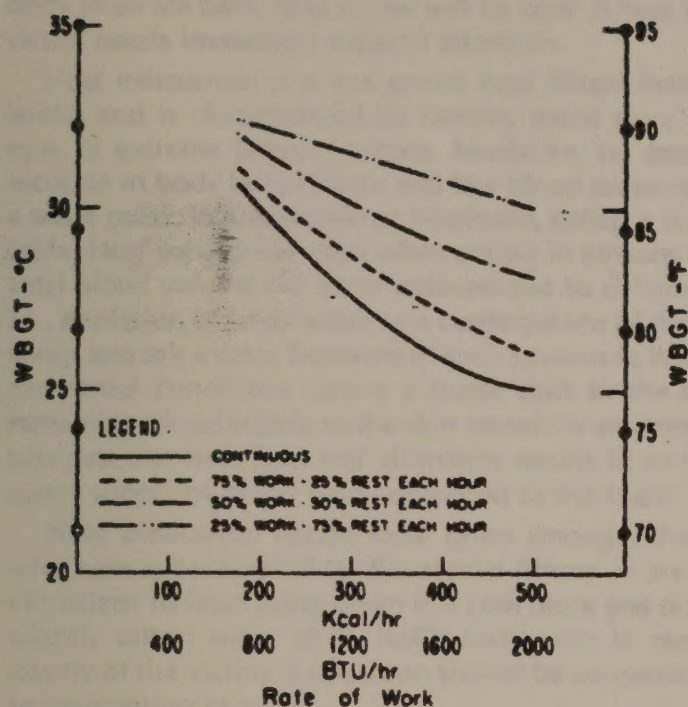


Figure 1 — Permissible Heat Exposure Threshold Limit Value

spent in the corresponding areas which are determined by a time study. Where exposure to hot environmental conditions is continuous for several hours or the entire work day, the time-weighted averages shall be calculated as hourly time-weighted averages, i.e., $t_1 + t_2 + \dots + t_n = 60$ minutes. Where the exposure is intermittent, the time-weighted averages shall be calculated as two-hour time-weighted averages, i.e., $t_1 + t_2 + \dots + t_n = 120$ minutes.

The permissible exposure limits for continuous work are applicable where there is a work-rest regimen of a 5-day work week and an 8-hour work day with a short morning and afternoon break (approximately 15 minutes) and a longer lunch break (approximately 30 minutes). Higher exposure limits are permitted if additional resting time is allowed. All breaks, including unscheduled pauses and administrative or operational waiting periods during work, may be counted as rest time when additional rest allowance must be given because of high environmental temperatures.

IV. Water and Salt Supplementation

During the hot season or when the worker is exposed to artificially generated heat, drinking water shall be made available to the workers in such a way that they are stimulated to frequently drink small amounts, i.e., one cup every 15-20 minutes (about 150 mL or 1/4 pint).

The water shall be kept reasonably cool (10-15° C or 50.0-60.0° F) and shall be placed close to the workplace so that the worker can reach it without abandoning the work area.

The workers should be encouraged to salt their food abundantly during the hot season and particularly during hot spells. If the workers are unacclimatized, salted drinking water shall be made available in a concentration of 0.1% (1 gram NaCl to 1.0 liter or 1 level tablespoon of salt to 15 quarts of water). The added salt shall be completely dissolved before the water is distributed and the water shall be kept reasonably cool.

V. Other Considerations

- Clothing:** The permissible heat exposure TLVs are valid for light summer clothing as customarily worn by workers when working under hot environmental conditions. If special clothing is required for performing a particular job and this clothing is heavier or it impedes sweat evaporation or has higher insulation value, the worker's heat tolerance is reduced, and the permissible heat exposure limits indicated in Table 1 and Figure 1 are not applicable. For each job category where special clothing is required, the permissible heat exposure limit shall be established by an expert.
- Acclimatization and Fitness:** Acclimatization to heat involves a series of physiological and psychological adjustments that occur in an individual during his first week of exposure to hot environmental conditions. The recommended heat stress TLVs are valid for acclimated workers who are physically fit. Extra caution must be employed when unacclimated or physically un-fit workers must be exposed to heat stress conditions.

Documentation for Heat Stress

Heat stress is defined as the total net heat load on the body with contributions both from exposure to external sources such as environmental, and from internal metabolic heat production. Man's exposure to heat stress conditions produces physiological responses or displacement of functions referred to as heat strain and characterized by an increase in: a) "core" or "deep body temperature"; b) heart rate; c) blood flow to the skin; and d) water and salt loss due to sweating. Conditions of excessive heat stress may occur either when the physical work is too heavy or the environment is too hot in relation to each other.

If work is to be performed under hot environmental conditions, the workload category (light, medium, heavy) of each job must be established⁽¹⁻⁴⁾ and the heat exposure limit maintained at or below the applicable Threshold Limit Value (TLV) in order to protect the worker from the risk of acute heat illnesses.

As a result of a process known as thermal homeostasis, man is normally able to maintain deep body temperature within acceptable narrow limits by means of a sophisticated thermoregulatory system. This is an autonomically controlled physiological response resulting in increased blood flow from sites of heat production in the muscles and deep body tissue to the cooler body surfaces where the heat is dissipated via the physical channels of conduction, convection, radiation and evaporation. If the heat gain exceeds the body's ability of heat dissipation, heat will be stored in the body as measured by its rising temperature.

Occasionally, as a result of the body's inability to cope with excess heat load, three heat illnesses may occur. Heat stroke is a state of thermoregulatory failure and is the most serious of the heat illnesses. Heat stroke is characterized by hot, dry skin, rapidly rising body temperature, collapse, loss of consciousness and convulsions. If deep body temperature approaches 41.1° C (106° F), the danger of heat stroke is imminent. Without prompt treatment, including removal of the victim to a cool area and reduction of the rapidly increasing body temperature, preferably by immersing the

body in an ice bath, heat stroke will be fatal. A heat stroke victim needs immediate medical attention.

Heat exhaustion is a less severe heat illness than heat stroke and is characterized by clammy moist skin, weakness or extreme fatigue, nausea, headache, no excessive increase in body temperature and low blood pressure with a weak pulse. Without prompt treatment, collapse is inevitable. Heat exhaustion most often occurs in persons whose total blood volume has been reduced due to dehydration, i.e., depletion of body water as a consequence of deficient water and salt intake. Exposure of such persons to hot environmental conditions causes a major shift in the body's remaining blood supply to the skin vessels in an attempt to dissipate the heat load and ultimately results in an inadequate supply of blood being delivered to the brain.

Heat exhaustion occurs most often among individuals who have a low level of cardiovascular fitness, or are unacclimatized to heat. Lying down in a cool place and drinking slightly salted water (0.1% NaCl) will result in rapid recovery of the victim. A physician should be consulted prior to resumption of work.

The third heat illness, heat cramps, is characterized by painful spasms in one or more skeletal muscles. Heat cramps primarily occur in persons who sweat profusely in heat without replacing salt losses. Resting in a cool place and drinking a cup of saline solution (0.9% NaCl) will alleviate the cramps rapidly.

The TLVs for heat stress are intended to provide guidelines on conditions under which it is believed that nearly all heat acclimatized workers dressed in their usual work uniforms and receiving adequate water and salt intake should be able to function effectively without exceeding a deep body temperature of 38° C (100.4° F).^(5,6) By general consensus among work physiologists, this temperature represents the value below which the body temperature must be maintained to minimize the risk of heat illness. Ideally, continuous monitoring of deep body temperature could assure that this limit would not be exceeded. This is not normally done, however, as the measurement of deep body temperature is impractical for routine monitoring of worker heat load. The TLVs for heat stress provide an index which combines measurable environmental factors for the purpose of predicting safe working conditions in a hot environment, i.e., conditions where worker deep body temperature would not exceed 38° C.

When permitting higher exposure limits than those recommended for continuous work, some provision for additional rest time becomes necessary. In general, when the work on a job is self-paced, the workers will accomplish this themselves by spontaneously limiting their hourly work load to 30-50% of their maximum physical performance capacity through the interspersing of unscheduled breaks or the setting of an appropriate work speed. In this manner, the *daily average* of their metabolic rate will seldom exceed 330 kcal/hr; however, within an 8-hour work shift, there may be periods where their hourly average metabolic rate will be higher. Under very hot conditions, any practice of allowing a compression of the work schedule rather than the interspersing of unscheduled breaks should be discouraged.

A comprehensive review of the numerous available heat stress indices by the TLV Committee in 1970, and a more recent review by the National Institute for Occupational

Safety and Health⁽⁷⁾ concluded that the Wet Bulb Globe Temperature Index (WBGT) is the simplest and most suitable currently available index. The numerical value for the WBGT Index can be calculated by one of two equations previously presented, depending on the presence or absence of solar loading. The methodology involved in the measurement of these parameters is explained by Minard.^(8,9)

The TLVs for heat stress will not afford adequate protection to unacclimatized workers, for without proper acclimatization and the resulting series of physiological and psychological adjustments that occur in an individual during this first week of exposure to a hot environment, tolerance to heat is significantly reduced.⁽¹⁰⁾ Further, adequate protection may not be provided during simultaneous exposure to certain sources of non-ionizing radiation including microwaves, radiofrequency and infrared radiation.

Certain persons, however, who demonstrate a higher than average tolerance to heat are able to withstand heat exposures higher than those permitted by this TLV and still maintain their deep body temperature below 38° C. For these workers, higher heat exposures are acceptable provided they have been appropriately identified through an acceptable medical selective test, such as the one presented by Shvartz,⁽¹¹⁾ and provided the workers are under medical surveillance.

Evidence presented by Lind⁽¹²⁾ shows that man can maintain his deep body temperature at a constant level, even though the environmental heat load increases up to a certain point which he called the Upper Limit of Prescriptive Zone (ULPZ). When the environmental temperature exceeds the ULPZ, then the deep body temperature becomes sensitive to changes in climatic conditions. No worker should be permitted to continue working when his deep body temperature exceeds 38° C.

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